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VECTOR ANALYSIS OF THE ELECTROCARDIOGRAM IN HYPERTENSION BEFORE AND IMMEDIATELY AFTER BILATERAL LUMBODORSAL SYMPATHECTOMY

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ONE OF the interesting results of the surgical treatment of essential hypertension has been improvement in the electrocardiogram. The contention that these changes indicate improvement in the heart itself, while plausible, may not be entirely without sophistry. A study of the electrocardiogram by means of vector analysis in cases of arterial hypertension was undertaken, therefore, in the hope of clarifying the mechanism of the electrocardiographic abnormalities in this disease; and especially in the hope of contributing to an understanding of the changes which may follow extensive lumbodorsal sympathectomy.[1,2]

The concept of semiquantitative analysis of the electrocardiogram by means of measurement of the area beneath the depolarization waves (QRS) and the electrical record of repolarization (ST-T) as a means of studying the time course of these events as they are projected on the frontal plane in standard limb leads has possible advantages over empirical interpretation. A larger experience and greater familiarity with the empirical method is its chief claim to superiority. The credibility of the concept of vector analysis and the ventricular gradient, first advanced by Wilson and co-workers,[3] is not subject, at the moment, to a great deal of controversy, but the available methods of measuring these vectors are not beyond criticism. The sources of error are manifold, but, crude as the methods may be, the semiquantitative analysis may give useful information.

The method used for measurement of the surface area of QRS and ST-T adopted in this study consisted of projection of the electrocardiogram by means of a stereopticon, and estimation of the number of small rectangles (4 microvolt seconds with the usual timing and standardization) included under the curves.

When the shape of the Q, R, and S waves permitted, the formula for area of a triangle was used. In our hands this method proved superior to planimetric measurement of the projected and retraced electrocardiogram. In part this may have been due to distortion by projection, in part to inherent inaccuracy of planimetry when used on curves as irregular as the electrocardiogram, and probably in no small measure to our inexpertness in the use of the planimeter. Enlargement by means of a hand lens is often adequate but inferior to the greater magnification made possible by projection.

The electrocardiograms of 106 patients were analyzed. It should be emphasized that these patients are a select group inasmuch as all had been accepted for, and had had, bilateral dorsolumbar sympathectomy by Dr. Reginald H. Smithwick. The series includes all types of electrocardiographic abnormalities save those showing intraventricular block or myocardial infarction, but the proportion of empirically normal or near normal records is higher than would be found in a general sampling of hypertensives. The electrocardiograms of patients who had received digitalis or quinidine were, of course, eliminated from the study.

RESULTS

The average age of the patients was 43.7 years, with a range of 25 to 55 years. Sixty were women and 46 were men. Normally the magnitudes of QRS (A-QRS) and the gradient (G) are smaller for women than for men, but the difference is slight. Sex difference has, therefore, not been taken into account, as separation would have made the subgroups too small for statistical treatment.

The cases were divided, after vector analysis was completed, into those whose preoperative records had been empirically interpreted as: (1) "within normal limits," (2) "borderline," (3) "left ventricular strain," and (4) "myocardial damage."

Although the vector analysis was based only on standard limb leads, the *empirical* interpretation was based upon multiple precordial and, in many cases, augmented unipolar limb leads as well.

Postoperative records to be reported upon here include only those in the immediate postoperative period. The usual interval was two weeks after completion of the second-stage splanchnicectomy. The desirability of limiting, so far as possible, the number of factors which might produce postoperative improvement is obvious, and study immediately after operation would seem to eliminate some of these factors. The preoperative values for the blood pressures given in the tables are an average of the pressures recorded over a period of several days after the level had stabilized, and do not include admission pressures, which were usually much higher. The postoperative value is the average of the recorded pressures for several days at the time the postoperative electrocardiogram was made.

The average preoperative and postoperative values for all 106 cases are shown in Table I. The average systolic pressure was 171 mm. Hg, and the average diastolic pressure 113 mm. Hg before operation. The average values approximately two weeks following completion of the second-stage splanchnicectomy

TABLE I.   AVERAGE VALUES IN 106 CASES

	PREOPERATIVE	POSTOPERATIVE	AVERAGE DIFFERENCE*
Systolic pressure	171	145	−25.7†
Diastolic pressure	113	96	−17.3†
Heart rate	78	83.5	+ 6.3
A–QRS (units)	8.3	7.9	− 0.37
Â–QRS (degrees)	23.0	27.9	+ 5.3†
G (units)	11.0	11.0	− 0.10
Ĝ (degrees)	27.6	30.0	+ 1.44

*In this and subsequent tables the statistical significance was determined by the "t" test for paired data.

† =Highly significant (Probability = 0.01 or less).

were 145 mm. Hg systolic and 96 mm. Hg diastolic.   The fall in both systolic and diastolic pressures is statistically highly significant.

Preoperatively the average A-QRS is large and G small, while the direction of both vectors is to the left of the average normal.   The only statistically significant change postoperatively was in the direction of QRS, which shifted toward the right.   G also showed a shift toward the right but the extent of this shift was not statistically significant.

TABLE II.   AVERAGE VALUES IN PATIENTS GROUPED ACCORDING TO THE PREOPERATIVE
ELECTROCARDIOGRAPHIC INTERPRETATION

PREOPERATIVE

	S. P.	D. P.	H. R.	A-QRS (UNITS)	Â-QRS (DEGREES)	G (UNITS)	Ĝ (DEGREES)	RATIO G/A-QRS
Within normal limits	170	112	78.4	6.9	25.5	12.0	28.6	1.86
Left ventricular strain	179	116	75.0	11.1	9.0	8.8	26.2	0.88
Myocardial damage	163	106	79.0	7.0	33.4	7.9	31.5	1.16
Borderline	175	114	79.0	8.1	35.9	14.1	29.7	1.41

POSTOPERATIVE

	S. P.	D. P.	H. R.	A-QRS (UNITS)	Â-QRS (DEGREES)	G (UNITS)	Ĝ (DEGREES)	RATIO G/A-QRS
Within normal limits	142	94	83.5	7.0	29.2	11.6	31.6	1.80
Left ventricular strain	153	100	80.0	9.9	14.7	10.0	20.9	1.10
Myocardial damage	146	94	89.0	8.2	38.4	10.3	39.3	1.29
Borderline	143	97	84.0	11.3	29.2	9.8	20.3	1.35

S.P., systolic pressure; D.P., diastolic pressure; and H.R., heart rate.

EMPIRICALLY NORMAL PREOPERATIVE ELECTROCARDIOGRAMS

Fifty-nine, or 55 per cent, of the preoperative records were considered to be within normal limits. The result of vector analysis in this group is shown in Table II. The average magnitude of A-QRS in *normal* adults is reported to be 6.3 units and that of G is 13 units.[4-6] The average for our group of hypertensives with "normal" electrocardiograms shows A-QRS to be slightly greater than normal, namely 6.9 units, and G to be slightly smaller than normal, 12.0 units. However, in no case was the upper limit of normal for A-QRS of 12 units significantly exceeded, and all values of the gradient were well above the lower normal value of 2.5 units.
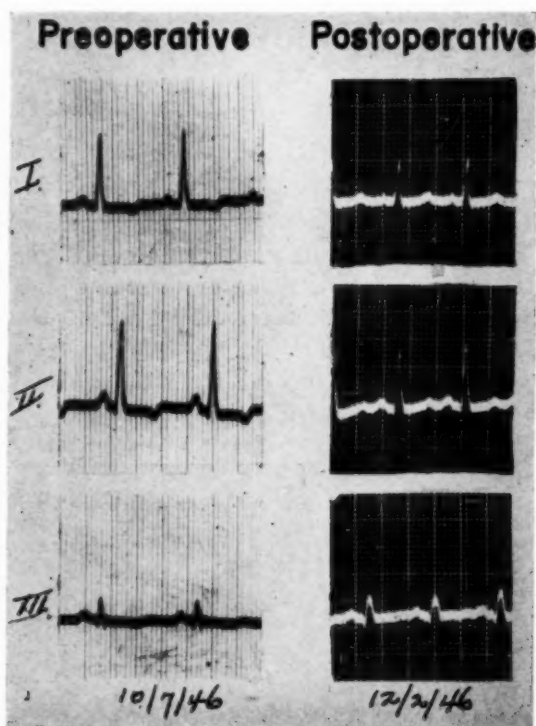

Fig. 1.—Pre- and postoperative standard limb leads of C. G., Case 1, Table II. The electrocardiogram has changed from the pattern of "left ventricular strain" to "within normal limits" in less than two weeks after the second-stage splanchnicectomy despite no change in the average basal blood pressure level. There was a marked decrease in the magnitude of G, due mainly, if not wholly, to an increase in heart rate. It seems obvious that the important cause of the change to normal is a marked decrease in the magnitude of A-QRS.

The *predicted* direction of Ĝ was calculated according to the method of Ashman and LaDue,[7] the direction of the longitudinal axis of the heart, Ĥ, being estimated from inspection of the electrocardiogram. In all but two cases of the "normal" group preoperatively, the observed Ĝ was within the limits allowed by Ashman and LaDue,[7] namely 15 degrees to the right or 23 degrees to the left of the predicted G, and in these two cases deviation was to the right

by 5 degrees or less.   Imperfections in present methods tend to discredit such slightly abnormal values.

The average *mean manifest* QRS in these otherwise normal records lies farther to the left than would be expected in a similar group of normal persons.

Results of analysis of the postoperative records in this group are also shown in Table II.   In three instances the record showed adverse changes, the postoperative interpretation being left ventricular strain in one, and borderline in two cases.   In many cases, even though the preoperative record was considered within normal limits, the postoperative T waves were "more normal" in form or amplitude.
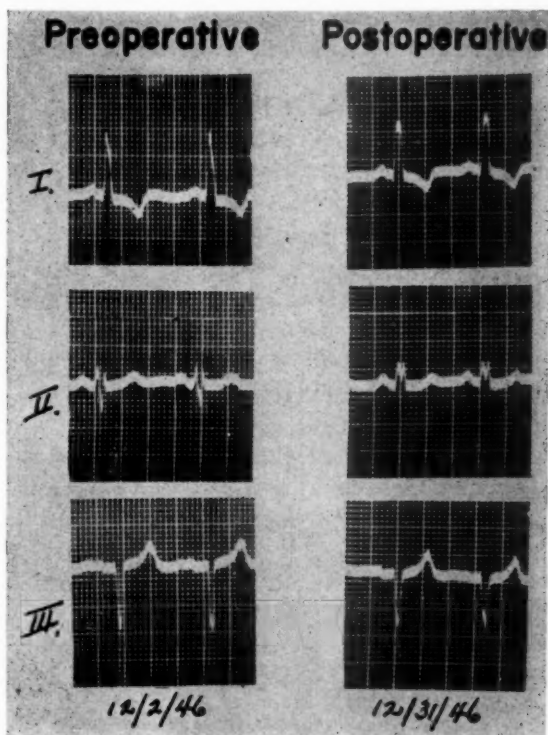

Fig. 2.—Pre- and postoperative standard limb leads of D. F., Case 4, Table II.   The pattern of "left ventricular strain" is unchanged in the immediate postoperative period despite a fall in the average basal systolic pressure from 200 to 140 mm. Hg, and in average basal diastolic pressure from 110 to 90 mm. Hg.   The magnitude of G increased over 100 per cent without improving the appearance of the T waves.

EMPIRICALLY ABNORMAL PREOPERATIVE ELECTROCARDIOGRAMS

Table II also shows the results of analysis of the cases in which preoperative electrocardiograms were empirically interpreted as abnormal.   The average figures for the group classified as showing left ventricular strain show a very large A-QRS and a relatively small G.   The average A-QRS was 11.05 units (normal average, 6 units), and the average G was 8.8 units (normal average, 13 units).   Postoperatively the magnitude of A-QRS decreased but was still

very large, and G increased slightly with a resultant increase of the ratio G/A-QRS from 0.88 to 1.10.

Consideration of some of the individual cases in this group is of interest. For example, one patient (C. G.), a 31-year-old man, showed a change from the strain pattern to normal with no alteration in blood pressure, the average value being 200 mm. Hg systolic and 130 mm. Hg diastolic before and after operation. The standard limb leads in this case are reproduced in Fig. 1. There was a marked decrease in the magnitude of A-QRS (from 16.0 to 7.4 units), and some shift to the right. G decreased from 11.3 to 8.0 units. The decrease of G, but not of A-QRS, is caused principally by the increased heart rate. The ratio, G/A-QRS, increased from 0.71 to 1.10. Another patient (E. W.), showed a fall in blood pressure from 160 mm. Hg systolic and 110 mm. Hg diastolic to 130 mm. Hg systolic and 90 mm. Hg diastolic. Despite the improvement in blood pressure and a favorable increase in G from 11.7 to 15.6 units (due mainly to slowing of the heart rate), there was no change in the electrocardiographic pattern.

Fig. 2 shows the standard limb leads in the case of a 52-year-old woman. The pattern of "left ventricular strain" is unchanged even though the blood pressure fell from 200 mm. to 140 mm. Hg systolic and 110 mm. to 90 mm. Hg diastolic, and G increased over 100 per cent.

The results of analysis of cases with preoperative electrocardiograms showing myocardial damage and those with borderline records are also shown in Table II. Since all the groups with abnormal records appear to be homogeneous, they will be analyzed together and subdivided according to whether or not the electrocardiogram improved postoperatively.

Table III shows average values for the group with abnormal records changing to, or toward, normal after operation (28 cases); the group showing no postoperative empirical improvement (19 cases); and, for comparison, the group with normal preoperative electrocardiograms (59 cases).

The average blood pressures before operation were the same in all groups, and all showed a significant and equal fall after operation. Although there is a higher average heart rate in the postoperative electrocardiograms in all groups, the difference is not statistically significant. Certainly the average change is far too small to seriously affect the vector analysis or the empirical interpretation.

The values for A-QRS and Â-QRS reveal important differences (Table III). Preoperatively, the average magnitude of QRS was slightly greater than normal in the group with "normal" electrocardiograms (6.9 units compared to an average normal value of 6.0 units). Those patients with abnormal preoperative records with change to, or toward, normal after operation showed an average preoperative A-QRS of 8.8 units, while those whose electrocardiograms did not improve had still larger A-QRS values with an average of 12.5 units. Furthermore, while the average value of A-QRS did not change significantly after operation in either the normal group or in the abnormal group with no postoperative improvement, there was a statistically significant decrease in the average value of A-QRS in the group showing postoperative improvement.

The average *magnitude* of the gradient, Table III, was smaller in those whose abnormal electrocardiograms were not favorably influenced by the operation

TABLE III.

	PREOPERATIVE	POSTOPERATIVE	AVERAGE DIFFERENCE
Systolic pressure (mm. Hg)			
Normal*	170	142	−27.3§
Improved†	169	144	−25.0§
Unimproved‡	179	155	−26.3§
Diastolic pressure (mm. Hg.)			
Normal	112	94	−18.5§
Improved	112	95	−15.9§
Unimproved	117	95	−17.7§
Heart rate			
Normal	78.4	83.5	+4.9
Improved	78.7	81.6	+2.4
Unimproved	82.2	84.9	+1.5
A–QRS (units)			
Normal	6.9	7.0	−0.2
Improved	8.8	7.5	−1.2¶
Unimproved	12.5	11.7	−0.8
Â–QRS (degrees)			
Normal	25.5	29.2	+4.6§
Improved	21.1	28.4	+8.0§
Unimproved	20.1	22.3	+2.3
G (units)			
Normal	12.0	11.6	−0.4
Improved	10.0	10.6	+0.6
Unimproved	9.7	9.8	−0.1
Ĝ (degrees)			
Normal	28.6	31.6	+2.5
Improved	25.0	30.5	+5.1
Unimproved	31.0	26.1	−4.3
Ratio G/A–QRS			
Normal	1.86	1.80	−0.03
Improved	1.21	1.47	+0.20§
Unimproved	0.89	0.88	−0.01

*The group of fifty-nine patients with preoperative electrocardiograms within normal limits.

†The group of twenty-eight patients with abnormal preoperative records becoming normal after operation.

‡The group of nineteen patients whose abnormal electrocardiograms showed no postoperative improvement.

§Highly significant pre- and postoperative average difference as determined by the "t" test. ("P" equals 0.01 or less.)

¶Just statistically significant difference average pre- and postoperatively. Actually, "P" in this instance was 0.04.

than in those with "normal" records (9.7 units compared to 12.0 units*).   However, the average magnitude of G preoperatively was essentially the same in the patients whose abnormal records became normal as in those whose records showed no empirical improvement, and in none of the groups was there any statistically significant increase in the average *magnitude* of the gradient postoperatively.   The average *direction* of the gradient, Ĝ, was essentially the same in all groups preoperatively, and none showed significant changes in the immediate postoperative period.   Seemingly this means that a small gradient, before operation, or its increase after operation, is not the chief cause of the electrocardiographic abnormalities or the determinant of improvement.   The same may be said, so far as

*Although this difference seems large, it is not certainly significant statistically, being more than twice but less than two and one-half times the standard deviation.

averages are concerned, for the *direction* of $\hat{G}$, although abnormal direction of $\hat{G}$ was present in a few cases. These cases will be discussed further below.

In the group with empirically normal preoperative records there were two instances of preoperative deviation of the observed direction of $\hat{G}$ from its predicted direction. The extent of the deviation in these cases is so small as to raise great doubt of its significance. Postoperatively, none of the cases in the "normal" group showed an abnormally deviated $\hat{G}$.

In those with preoperative records showing left ventricular strain, $\hat{G}$ was abnormally deviated in five cases. In two cases the observed direction of $\hat{G}$ deviated to the right from the predicted direction by 21 and 19 degrees, respectively. Since A-QRS was large in both cases, the upper limit of allowable deviation is 12 degrees to the right.[7] It is a matter of opinion whether the accuracy of the methods involved warrants attributing significance to this degree of divergence. We are inclined to believe that it does not. In the remaining three cases the amount of deviation was large, being 45, 65, and 118 degrees to the right. There can be little doubt that these figures represent a significant deviation of $\hat{G}$ from the normal.

Postoperatively one case showed an increase in the deviation of $\hat{G}$ from 23 degrees to the left (the preoperative deviation) to 35 degrees to the left. The preoperative figure is below the upper limit of allowable deviation to the left at a heart rate of 80, and the postoperative value only 12 degrees above the limit. The postoperative value for A-QRS was very large in this case (26.5 units). Since prediction of the direction of $\hat{G}$ involves the use of a table with a maximum value of A-QRS of 11 units,[7] the error in extrapolation may readily account for this degree of deviation.

One of the cases with a large preoperative deviation (45 degrees to the right) showed no deviation from the predicted direction in the postoperative record although empirically the electrocardiographic interpretation was unchanged. In the other two cases the direction of G postoperatively remained abnormally deviated to the right, although to a lesser degree.

In the myocardial damage group the gradient was abnormally deviated in three cases. In one of these the deviation was 69 degrees to the left of the predicted $\hat{G}$. Postoperatively there was close agreement between the observed and predicted direction of $\hat{G}$ (a difference of 4 degrees) and the postoperative record had become empirically normal. A second case showed a deviation of the observed from the predicted direction of $\hat{G}$ of 31 degrees to the left preoperatively and 32 degrees to the left postoperatively. Both of these values are only slightly, if any, above the allowable range to the left at these heart rates, and are of doubtful significance. The third case showed an abnormal deviation of $\hat{G}$ to the right of significant magnitude (38 degrees). This deviation of G disappeared postoperatively and empirically the record became "normal."

In the borderline group, $\hat{G}$ was abnormally deviated in two cases, the deviation being to the left in both (78 and 64 degrees). In one the deviation disappeared postoperatively, and in the other it persisted.

No case showed definitely significant deviation of $\hat{G}$ in the postoperative record unless such deviation had been present before operation. That is to say, in the 106 cases, no instance of primary T-wave abnormality due to change in the direction of the gradient developed postoperatively.

DISCUSSION

The cause of the phenomenon, the normal ventricular gradient, is not known. It has been attributed to more rapid recovery of the subepicardial than of the subendocardial fibers.[8] The form and direction of the T wave depends, on the one hand, upon the direction and magnitude of QRS, and on the other hand, on the direction and magnitude of the gradient. T-wave abnormalities due to unusual form of QRS have been called "secondary" T-wave changes, while those associated with changes in the gradient due to anatomical or physiological changes in the myocardium itself are designated "primary" T-wave abnormalities.[5]

It is apparent that T-wave inversion may occur by, (1) increasing the size of QRS, the size and direction of the gradient remaining the same, (2) decreasing the magnitude of the gradient, or (3) altering the direction of the gradient. The great majority of T-wave abnormalities encountered in this group of hypertensive patients was of the "secondary" type.

At the beginning of this study it was thought possible that abnormal deviation of $\hat{G}$, that is, "primary" T-wave abnormalities might be used as one of the criteria for excluding the patient from splanchnicectomy. This proved not to be the case, for not only did several patients with an abnormally deviated gradient show empirical changes to normal in the electrocardiogram but also the gradient deviation disappeared in the postoperative record.

T-wave changes in hypertenson have received more attention than the QRS complex. This has largely resulted from the knowledge that left axis deviation is determined more by the position of the heart in the thorax than by ventricular size. The present study seems to indicate that the *mean manifest* A-QRS as it is projected on the frontal plane may be the primary alteration occurring in hypertension, and that T-wave inversion is secondary to an increase in the magnitude of A-QRS (augmented, perhaps, by a decrease in the magnitude of the ventricular gradient). The average figures given in Table III seem to show that increasing abnormality of the electrocardiogram is associated with an increasingly large A-QRS and, as this value becomes larger, the chance of empirical change toward normal in the immediate postoperative record diminishes. There are, however, individual exceptions to this rule. In the group with abnormal preoperative records which became normal following operation, values for A-QRS as high as 19.5 units were found, while in the group whose electrocardiograms showed no empirical improvement there were some with values for A-QRS of 10.0 units or less.

Despite the fact that average preoperative gradient values do not show a significant difference between the group which became normal and the group which did not, and in individual cases the value for the gradient increased as much as 100 per cent without favorably influencing the form of the electro-cardiogram, the gradient *is* of importance in determining T-wave direction when

its relative magnitude is expressed as the ratio G/A-QRS.   The average preopera-
tive ratio for the group with "normal" records was 1.86.   The group whose
abnormal records subsequently became normal showed an average preoperative
ratio of 1.32, while the preoperative average for the group showing no empirical
improvement was only 0.89.   The diminishing ratio of G/A-QRS was due to an
increasing A-QRS with G remaining more or less constant, i.e., failure of G to
increase as A-QRS increased.*   Postoperatively the average ratio for the group
who showed changes to normal had increased to 1.46 while the average for the
group showing no empirical improvement remained at 0.89.   This improvement
in the average ratio was due wholly to a decrease in A-QRS and not to any increase
in G.   It would appear, therefore, so far as predicting immediate improvement
in the electrocardiogram following extensive lumbodorsal sympathectomy is
concerned, that both the absolute value for A-QRS and the ratio of G to A-QRS
are to be reckoned with.

The factor of primary importance in determining the magnitude of QRS
in normal persons is the position of the heart in the thorax.[6,7]   Since alteration
of the QRS in both direction and magnitude appeared to be of importance in
the genesis of the electrocardiographic abnormalities preoperatively as well as
in the postoperative changes, it naturally occurred to us that positional changes
might be involved.

That there was indeed a postoperative change in the electrocardiographic
position of the heart seems likely since there was a change in the average course
of all the vectors in the same direction.   The average shift in Â-QRS for all cases
was 5.3 degrees to the right, in Ĝ 1.4 degrees to the right, and in Ĥ 1.7 degrees
to the right.   The shift was not statistically significant for either Ĝ or Ĥ, but
since all changed in the same direction it seems logical to assume that it may
have some meaning.   The shift in Â-QRS to the right occurred in all subgroups
but the extent of the shift was statistically significant only for the groups with
normal preoperative electrocardiograms and in those with abnormal records
changing to or toward normal after operation.   The group with abnormal pre-
operative records who did not show empirical improvement in the immediate
postoperative period showed a statistically insignificant shift to the right post-
operatively.

If the change in the position of the heart is of the importance that it might be,
it is not of the type associated with elevation or depression of the diaphragm.
The simple experiment of recording the electrocardiogram in several patients with
the early changes of the strain pattern (those most likely to show immediate post-
operative improvement) in full inspiration and full expiration established this
fact.   In one such case with the "strain" pattern uninfluenced by the effect of
full inspiration and expiration, the electrocardiogram became normal in the im-
mediate postoperative period.   This, of course, does not detract from the im-
portance of change in position, for rotation around any or all of the three axes

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*This suggests rotation of the heart around its longitudinal axis.   The vectors Â-QRS and Ĝ are
projections of the spatial vectors SÂ-QRS and S Ĝ and the relative size and direction of these spatial
vectors are such that rotation around the longitudinal axis of the heart will result in greater foreshorten-
ing (or the opposite) of A-QRS than of G.

of the heart may occur in numerous combinations not easily reproducible by simple experimental procedures. Since the effect of the extremes of respiration is upon rotation around the anteroposterior axis and, almost certainly, upon the longitudinal axis of the heart, and since such rotations appear to be without effect upon the appearance of the electrocardiogram, it seems likely that rotation around the remaining (transverse) axis of the heart is the movement of import-ance. This, in fact, agrees with theoretical considerations. Displacement of the apex to a more forward position in the thorax increases the net area of QRS, and a more backward position decreases A-QRS.[6] The cause of such move-ments, if they occur, is not known. The size and shape of the heart almost certainly would be concerned. Some of the more obvious other possibilities are related to the width, length, elasticity, and internal pressure of the great vessels at the base of the heart. In any event it has seemed worth while to point out the possibility that the electrocardiographic abnormalities in hypertension and, in particular, the change to normal immediately after sympathectomy, may be due to factors not heretofore adequately considered. It is no longer justifiable to refer to the T-wave inversion of the strain pattern as due to coronary insufficiency until more impressive evidence than is now available can be pre-sented.

SUMMARY AND CONCLUSIONS

1. Measurement of the mean manifest magnitude of QRS (A-QRS) and its direction (Â-QRS), and the magnitude and direction of the ventricular gradient (G and Ĝ respectively) was completed in 106 cases of essential hyperten-sion before and after extensive lumbodorsal sympathectomy. The study dealt only with changes encountered in the immediate postoperative period. The cases were divided into groups on the basis of the empirical interpretation of preoperative electrocardiograms, there being fifty-nine cases with records within normal limits, twenty-three showing left ventricular strain, thirteen with myo-cardial damage, and eleven with records considered to be borderline.

2. In general, the conventional interpretation of "within normal limits" was in agreement with vector analysis. However, the average values of the vec-tors showed leftward deviation of both Â-QRS and Ĝ, with larger A-QRS and smaller G than average normal values. Following operation, both Â-QRS and Ĝ in the "normal" group showed an average shift to the right but only the change in Â-QRS was statistically significant. The *magnitude* of neither A-QRS nor G was significantly altered after operation.

3. The group with abnormal records (forty-seven cases) was divided in the postoperative period according to whether the electrocardiograms had shown empirical improvement or not. There were twenty-four patients whose post-operative records were interpreted as being within normal limits and four other patients showed changes toward normal. *Thus 60 per cent of patients with ab-normal preoperative electrocardiograms showed empirical changes to or toward normal within two weeks after completion of bilateral lumbodorsal sympathectomy.*

This postoperative empirical improvement was associated with an average, statistically significant, shift of Â-QRS toward the right. The *magnitude* of

A-QRS was significantly reduced in the improved group but not in the unimproved, while the *magnitude of the gradient* showed no change in the average value for either group.

The average preoperative value for the magnitude of A-QRS was much larger for the group showing no improvement and showed only a slight, and statistically insignificant, decrease after operation, whereas the group showing postoperative electrocardiographic improvement manifested a statistically significant reduction in A-QRS.

4.   All groups were found to have essentially the same average preoperative blood pressure and all showed an equal, and highly significant, decrease in the postoperative period.   Improvement of the electrocardiogram in the immediate postoperative period is thus independent of the average initial basal level and the average fall of blood pressure.

5.   The genesis of the electrocardiographic abnormalities in the standard limb leads of hypertensive patients appears to be, in this series at least, dependent upon an increase in the mean manifest area of QRS.   On the basis of theoretical considerations it is suggested that both the initial increase in A-QRS and the postoperative decrease in A-QRS, with T-wave alterations secondary to such changes may be dependent upon change of position of the heart in the thorax.

The precise definition of which of the three axes of the heart may be primarily involved is unknown, but several considerations lead to the suggestion that rotation around the transverse axis with movement of the apex forward and backward is of great importance.   The cause of such positional changes is unknown.

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A CASE OF RECIPROCAL BEATING WITH EVIDENCE OF REPETITIVE AND BLOCKED RE-ENTRY OF THE CARDIAC IMPULSE

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R E-ENTRY of the cardiac impulse is a hypothetical mechanism of disturbances of the cardiac rhythm such as premature systoles, paroxysmal tachycardia, auricular fibrillation, and auricular flutter. However, the simplest and most convincing evidence of a re-entry mechanism in the human heart is the phenomenon of reciprocal beating in cases of auriculoventricular nodal rhythm with delayed retrograde conduction. A number of unquestionable cases of reciprocal rhythm have been reported.[1-17] The conditions of the tissues responsible for re-entry have been studied experimentally[18-20] and reciprocal beating has been reproduced in the dog's heart.[21,22] In this report, an additional clinical case† of reciprocal beating is presented because of two unusual features: a) Evidence of repetitive re-entry giving rise to a circulating movement as already described[24,25] in a few instances of reciprocal beating, and b) evidence of re-entry of the impulse without reciprocal beating of the ventricles, viz., evidence of discharge of the A-V nodal pacemaker by the re-entrant impulse, which fails to elicit a ventricular response due to its blockage below the nodal pacemaker.

The electrocardiograms were obtained on a 76-year-old white woman‡ with diabetes mellitus, hypertensive arteriosclerotic heart disease, and chronic congestive failure. The patient died in congestive failure a year later and the autopsy performed by Dr. O. Saphir of the Department of Pathology revealed the following findings of the cardiovascular system: generalized arteriosclerosis, marked coronary sclerosis and occlusion of the anterior descending branch of the left coronary artery; recent and old infarcts of the left ventricle with aneurysmal dilatation; old healed valvular endocarditis; hypertrophy and dilatation of the heart; and marked chronic hyperemia of the lungs, liver, and kidneys. A histological examination of the conduction system was not performed.

During her hospital admission from April 26 to May 23, 1945 a number of long records were taken. Certain sections were selected for illustration in Figs. 1 to 5. The A-V nodal rhythm present in most of the records (Figs. 1,b to 5) developed under digitalis therapy, although only small doses of digitalis were given and no clinical signs of digitalis intoxication were present. The logical

TABLE I. NUMBER OF SPONTANEOUS CARDIAC IMPULSES WITH SINGLE OR MULTIPLE RESPONSES OF THE VENTRICLES AS RECORDED IN THE ENTIRE SERIES OF TRACINGS

IMPULSES	DIAGRAM (FIGURE NUMBER)	DATE OF TRACING									TOTALS	
		4/28 A.M. (FIG. 1,b)	4/28 P.M. (FIG. 3, a,b, FIG. 4,c)	5/1	5/2 A.M.	5/2 P.M. (FIG. 2)	5/4 (FIG. 4,b)	5/8 (FIG. 4,a)	5/12	5/28 (FIG. 5)		
A-V nodal impulses												
No re-entry due to short R-P	6,a to 6,e	14	65		81	36			73	44	313	
No re-entry due to interference of sinus impulse	8,d to 8,g	2	9	72	49	3		1	6	59	201	514
Single re-entry, conducted (reciprocal beat)	6,a		9	1	10	10				77	107	
Single re-entry blocked below nodal pacemaker	6,b	15			80	33			75		203	310
Double re-entry, second conducted	6,d		3*								(3)*	
Double re-entry, second blocked below nodal pacemaker	6,c		54	74	2						130	
Double re-entry, second blocked above nodal pacemaker	6,e and g		15	10	31	7	2	13	8	8	94	224
Triple re-entry, last blocked below nodal pacemaker	6,d		3*								3*	
Triple re-entry, last blocked above nodal pacemaker	6,f						73				73	76
Quadruple re-entry, last blocked above nodal pacemaker	6,d		3*								(3)*	
Sinus impulses reaching the ventricles										12	12	
Number of recorded cardiac impulses		31	155	157	253	89	75	14	162	200		1136

*Identical instances.

development of our analysis of this case can be followed by studying the figures in the sequence presented.   The number of spontaneous cardiac impulses with single or multiple response of the ventricles as recorded in the entire series of tracings is listed in Table I.   Various forms of single and multiple re-entry, as observed throughout the tracings, are illustrated diagrammatically in Fig. 6.
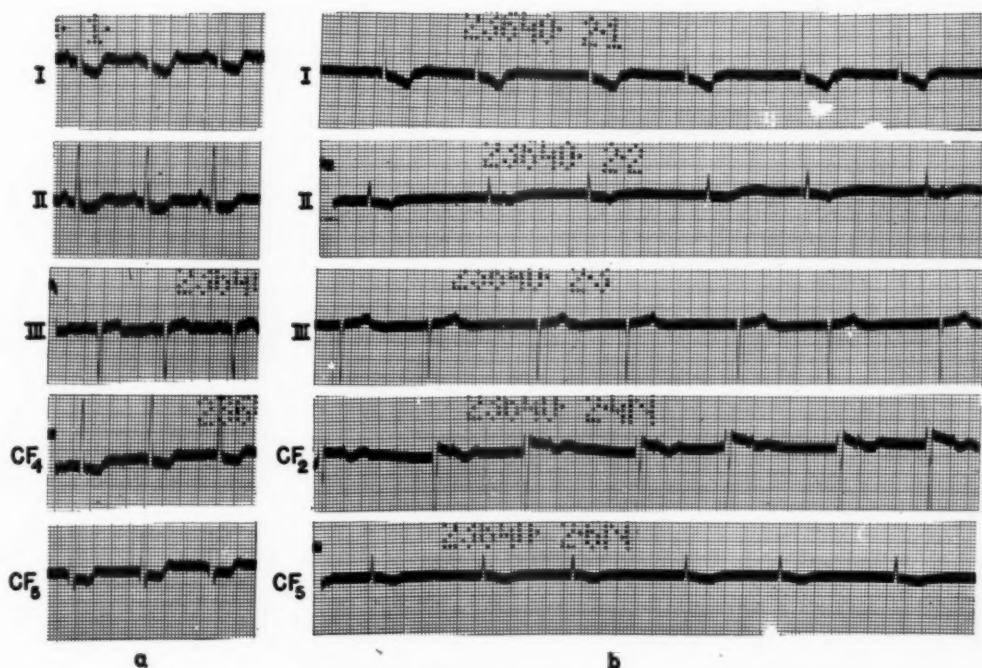

Fig. 1.—*a*, Record taken Feb. 10, 1945 (two months before admission to the hospital).

Sinus rhythm with regular rate of 80 and P-R of 0.14 second.   The ventricular complexes show evidence of left heart strain and ST-T changes attributable to digitalis.   Note that the P waves are upright in all limb leads.

b, Record taken on the morning of April 28, 1945.

Both ventricular and auricular complexes are spaced irregularly with alternation of longer and shorter intervals.   The P waves follow QRS at varying intervals, the shorter R-P occurs after the longer R-R.   Note the varying contour of P, best seen in Lead II.   The second and last P in this lead is upright and corresponds to a sinus P of Figure 1,*a*.   The first, third, and fifth P waves are inverted and retrograde in origin.   The fourth P represents a fusion P.   In Lead CF_2, all P waves are large and diphasic ($\mp$), indicative of retrograde conduction.   For interpretation see Fig. 2.

DISCUSSION

In the 610 recorded instances of re-entry, the following variations were observed (Table I, Fig. 6):

1.   Re-entry within the A-V node with block of the cardiac impulse below the point of its origin in 310 instances.   This block below the nodal pacemaker was assumed to be complete in 203 instances (Fig. 6,*b*) and became recognizable merely by a delay of the following spontaneous nodal discharge.   In 107 instances, the block seemed to involve conduction through the A-V junction and over the more vulnerable right bundle branch system[26] and manifested itself in

delayed conduction to the ventricles and in aberrant contour of the reciprocal beat (Fig. 6,a).

2. In 224 instances, a second re-entry or an attempt at a second re-entry was assumed. In 130 instances, the nodal pacemaker was reached and discharged by the second re-entrant impulse leading to an abrupt and marked prolongation of the nodal interval (Fig. 6,c and f). In 94 instances, the impulse obviously did not complete the whole re-entry path, but was blocked at different levels below the point of re-entry (Fig. 6,e and g). Such a blocked second re-entry had to be postulated where the nodal beat occurring after the first re-entry showed a prolonged retrograde conduction time (R-P interval). Due to this mechanism, blocked first re-entry as well as persistent and blocked second re-entry were assumed to be concealed in an apparently perfectly regular nodal rhythm (Fig. 4,a and Fig. 6,g). Similarly, persistent bigeminal rhythm occurred as a result of double re-entry with transmission of the first to the ventricles (Fig. 4,b and Fig. 6,f).

3. Triple and quadruple re-entry (Fig. 6,d and f) was assumed in 76 instances, three of them (Fig. 4,c and 6,d) with two reciprocal beats in succession and the appearance of a second retrograde P wave.

The re-entry mechanism: The conditions responsible for the rare phenomenon of reciprocal beating have been elucidated experimentally by Schmitt and Erlanger[19] and later by Ashman and Hafkesbring[20] and are illustrated in Fig. 7. The presence in the A-V junction of an unequally depressed region leads to delayed retrograde conduction (heterodromia) of the nodal impulse over the fibers with less marked depression and to unidirectional block (monodromia) in the fibers with more marked depression. Having passed the region of depression over less involved fibers, the retrograde nodal impulse now penetrates from above into the fibers which were blocked for retrograde conduction and returns to the point of its origin. Provided the time of retrograde conduction is long enough, the re-entrant impulse will find the pacemaker already outside its refractory state and can discharge the pacemaker for a second time. The reciprocal impulse may then be conducted to the ventricles or may be blocked below the nodal pacemaker. However, at the same time another attempt at retrograde conduction may occur and, depending on the same factors—namely recovery of fibers responsible for retrograde conduction—this second retrograde impulse may or may not again reach the point where penetration into the pathway for forward conduction is possible. When two or more re-entries occur in succession neither the rate of conduction nor their actual path need be identical for every individual circuit.[27] It would appear that a slower rate of retrograde conduction might permit re-entry at a lower level, thus shortening the path.

Single re-entry: In general, premature beats appearing during persistent nodal rhythm, as seen in our tracings, may be due to the discharge of another ectopic pacemaker, to "ventricular capture" by the primary pacemaker, or to reciprocal beating. The first two possibilities can be excluded in our case, since premature systoles would not explain the rest of the arrhythmia present in the tracings and since there are no signs of sinus activity in Fig. 2 to Fig. 4 necessary

to assume ventricular captures.   On the other hand, reciprocal .rhythm appears likely since definite signs of retrograde conduction from the A-V node to the auricles are present throughout the records and the premature beats appear after delayed retrograde conduction.   The re-entrant nodal impulse discharges the nodal pacemaker and thus accounts for the delayed occurrence of the following nodal beat.   During its conduction to the ventricles, the re-entrant impulse must be markedly retarded to give rise to beats usually seen in conduction defect of the right bundle branch system.   In Fig. 2,*a* and *b*, the occurrence of reciprocal beats after nodal beats with a long R-P interval is the clue for the explanation of long R-R intervals which do not contain a reciprocal beat.   Evidently, here, too, re-entry was attempted, the re-entrant impulse discharged the pacemaker but was blocked below it and thus failed to elicit a ventricular response.   The blocked reciprocal impulse became manifest merely by causing a disturbance in the rhythmic discharge of the nodal pacemaker.   Thus, either partial or complete block of the re-entrant impulse, both below the pacemaker, can be assumed in the record.

The rate of the nodal pacemaker can be determined.   It is indicated by the duration of the shorter R-R intervals (e.g. in Fig. 2: 1.00 to 1.08 seconds).   The assumption of a constant rate of forward conduction of the nodal beats also permits the calculation of the re-entry time, i.e., (a) the time for retrograde conduction of the impulse from the nodal pacemaker up to the point of re-entry plus (b) the time for forward conduction of the re-entrant impulse from the point of re-entry to the point of origin of the nodal beats.   The sum (a+b) equals the difference between the long and short R-R intervals (0.24 to 0.28 second in Fig. 2) if we neglect a possible depression of the nodal pacemaker after its discharge by the re-entrant impulse.   The shortening of the R-P interval after a single re-entry will be explained later when double re-entry is discussed.   Slight differences in the rate of the spontaneous discharge of the nodal pacemaker have to be assumed to account for the differences in R-R and R-P intervals in the various tracings.   By contrast, the value for the re-entry time, as calculated above for Fig. 2, remained fairly constant (0.24 to 0.30 second).

Double re-entry: As stated before, re-entry occurs when the retrograde conduction is sufficiently delayed to permit recovery of the re-entry path.   Such a delay in retrograde conduction of the nodal impulse occurs whenever the path for retrograde conduction is traversed by two impulses in quick succession. Different pathways have to be assumed for the conduction of the retrograde and re-entrant impulse (Fig. 7).   The short duration of R-P of the nodal impulse following a reciprocal beat, as described in Fig. 2 and Fig. 6,*a* indicates recovery of the fibers used for retrograde conduction at the time when conduction of the re-entrant impulse occurs over fibers used for forward conduction.   If on the other hand, as seen in Fig. 3,*a*, 4,*a*, 6,*e* and *g*, the nodal beat following a re-entry beat again shows a prolonged R-P, we have to assume that the preceding reciprocal impulse in attempting a second re-entry entered the path for retrograde conduction of the nodal impulses for a short distance.   An alternative explanation for the R-P prolongation of the nodal beat following re-entry would be the assumption that the re-entrant impulse, before reaching and discharging the nodal pace-

Fig. 2.—Record taken on the afternoon of May 2, 1945. Lead CF₂. Single re-entry.

The mechanism of the conduction disturbance is illustrated in the diagram below the electrocardiogram. The conventions are those used customarily. A-V represents the spread of the impulse through the auriculoventricular junction between the auricles (A) and the ventricles (V). Oblique lines at different angles indicate the varying speed of impulse conduction through the A-V junction; the short lines at right angles to the oblique lines, blockage of the impulse. The broken lines indicate aberrant conduction within the ventricles. The values for P-P, R-P, and R-R intervals are given in hundredths of a second.

A-V nodal rhythm with delayed retrograde conduction to the auricles is present. No sign of sinus activity is seen. When R-P increases from 0.20 to 0.28 second, re-entry of the retrograde impulse occurs. The re-entrant impulse discharges the A-V node and is either blocked below it (long R-R intervals) or gives rise to a ventricular complex (reciprocal beat) with aberrant conduction and fixed coupling of 0.56 second. Note that in a the R-R intervals, containing a reciprocal beat, equal the long R-R intervals containing the blocked reciprocal impulse. Also note the shortening of R-R following every re-entry. The allorhythmia ("bigeminal rhythm") in b is due to blockage of a reciprocal impulse after every second nodal beat. Discussed in text.

maker, also penetrates into the lower part of the already recovered portion of the fibers used for retrograde conduction.   The unique phenomenon of progressive *shortening* of successive R-P distances in the first three couples of Fig. 3,*a* suggests that the re-entrant impulse penetrated progressively less into the retrograde pathway.   Whereas an unsuccessful attempt at a second re-entry may be postulated after each of the first nodal beats of Fig. 3,*a*, completed second re-entry with return to and discharge of the pacemaker can be assumed after the fifth nodal beat of this figure to account for the long R-R interval of 1.16 seconds after the fourth reciprocal beat.   Again as an alternative but less likely explanation, one could assume that the nodal pacemaker instead of being discharged for a second time by a second sweep of the re-entrant impulse is discharged only once by a re-entrant impulse which is conducted with a considerable delay along the fibers used for retrograde conduction.   Such a mechanism would not explain the appearance of a second retrograde P wave as seen in Fig. 4,*c*.   The calculated time for re-entry of the first three reciprocal beats in Fig. 3,*a* is 0.28, 0.30, and 0.28 second, respectively, that for the assumed double re-entry in the same tracing 2×0.31 second $(0.56 + 1.16 - 1.10 = 0.62)$.   This is in accordance with the assumption of double re-entry, although in the case of double re-entry the second spread may not take place along a precisely identical path or with an identical speed of conduction of the first re-entry.   Similar calculations may be applied also to Fig. 3,*b*.

Multiple re-entry: Examples of multiple re-entry are illustrated in Fig. 4. Figure 4,*b* shows an instance of double forward and triple retrograde conduction. Reciprocal beats identical with those shown in previous records follow every nodal beat, giving rise to bigeminal rhythm.   The pause (1.12 to 1.16 second) following the premature beats is longer than the nodal interval (1.00 to 1.08 second) present that day (May 4, 1945) in the rest of the tracing (not shown).   If we subtract the latter interval from the interval between two nodal beats which contain a reciprocal beat (1.64 to 1.68 second) we obtain a value of 0.64 to 0.68 second, i.e., approximately double the re-entry time calculated in previous records.   As indicated in the diagram, double re-entry with an attempt at a third one after every nodal beat had to be assumed.   The third uncompleted re-entry was postulated to account for the failure of the subsequent R-P to shorten, leading to persistent re-entry after every nodal beat (Fig. 6,*f*).

In Fig. 4,*c*, five different instances of retrograde conduction of the nodal pacemaker with and without re-entry can be seen in a single tracing.   Varying and probably more marked depression in the A-V junction on this day is also indicated by the slower rate of the nodal pacemaker in Fig. 4,*c*, the interval between two successive nodal beats measuring 1.20 seconds compared to 1.00 to 1.08 seconds in Fig. 2.   Both these tracings were taken on the afternoon of April 28 in quick succession.   In Fig. 4,*c*, the beat initiating the inter-nodal interval of 1.20 seconds has an R-P of 0.22 second which is too short to permit re-entry. Hence, the interval of 1.20 seconds indicates the rate of the pacemaker for this tracing.   Calculating the re-entry time by subtraction as in previous figures, single re-entry can be assumed for the preceding, and double re-entry with an

attempt at a third one for the following group of coupled beats. However, the
re-entry times are longer (0.33 to 0.44 second) than those in Fig. 1,*b* to 3. In
the first group of Fig. 4,*c*, the usual sequence—nodal beat, retrograde P wave,
reciprocal beat—is followed by another short coupled ventricular complex, which
differs only slightly in the shape of T from the complexes of nodal origin. Another
diphasic ($\mp$) P wave suggesting retrograde conduction in spite of some difference
in contour precedes this beat by 0.08 second. Two more such instances of two
retrograde P waves "sandwiched" between two short coupled beats in succession
were observed in the long tracings of this day, but in none of the subsequent
records. Appearance of a second retrograde P wave in these instances may be
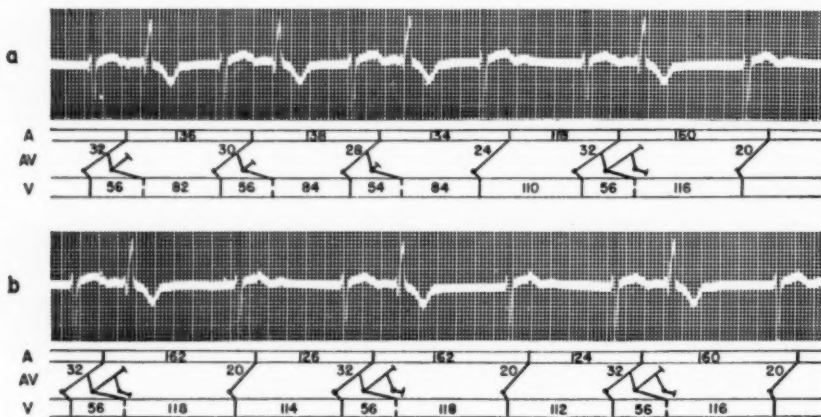considered as confirmatory evidence of the assumed repetitive re-entry in our
case.

Fig. 3.—Records taken on the afternoon of April 28, 1945. Lead CF₂. Double re-entry.
    Conventions as in Fig. 2. In addition, varying lengths of oblique lines, representing blocked im-
pulses, indicate the varying distance to which the impulse penetrates into the path for retrograde con-
duction in an attempt at a second re-entry.
    At the beginning of *a* three reciprocal beats appear in succession. Note the progressive shortening
of the R-P distance from 0.32 to 0.28 second explained by the different extent of retrograde conduction
of the preceding re-entry. The fourth nodal beat giving rise to a retrograde P wave after only 0.24
second is no longer followed by re-entry. A fourth reciprocal beat at the end of this tracing and three
others in *b* are followed by long nodal intervals, due to a second discharge of the pacemaker by a second
re-entry which is blocked below the pacemaker. Discussed in text.

However, objections may be raised to the interpretation of the second of the
coupled beats as reciprocal in nature, since it does not show the aberration of
ventricular conduction present in the first reciprocal beat. Recovery of the right
bundle branch system, not used by the first re-entry, and its shorter refractory
period due to the short preceding pause may explain the normal appearance of
the second reciprocal beat. The same phenomenon has been observed with
auricular premature systoles occurring in pairs. Block of the second retrograde
impulse and conduction to the auricles of the third is indicated in the diagram.
This was postulated to avoid an improbable retrograde conduction time of
0.70 to 0.80 second and in accordance with a re-entry time of 0.38 second [(0.58
+ 0.60 + 1.16 − 1.20) : 3]. Furthermore, the interval (0.58 + 0.60) between the
nodal and second reciprocal beat is about the same as the assumed simple nodal

interval (1.20 second) in the tracing. This might suggest interpolation of the first reciprocal beat between two nodal discharges; however, it would imply a protection block of the nodal pacemaker against the re-entrant impulse[22] and no evidence of such a mechanism is available throughout the rest of the tracings.
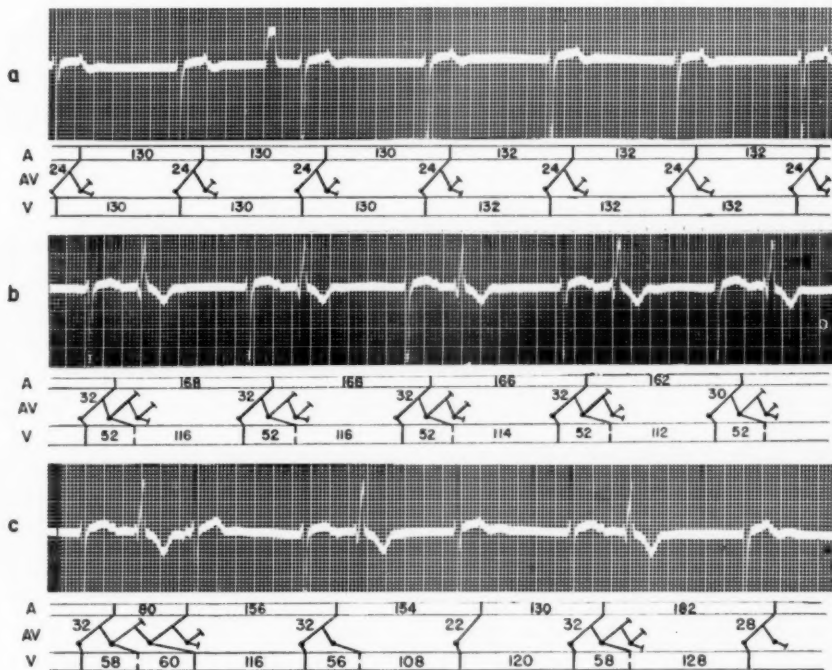

Fig. 4.—Lead CF_2. Conventions as in Fig. 3.

a, Record taken May 8, 1945. Concealed re-entry.

Apparently undisturbed nodal rhythm with constant prolongation of retrograde conduction time (0.24 second), but actually the slow ventricular rate—as compared with Fig. 2—indicates re-entry after every nodal beat with block below the pacemaker. Retrograde penetration of the re-entrant impulse is postulated to explain the lack of shortening of R-P following re-entry (compare with Fig. 2 and Fig. 3).

b, Record taken May 4, 1945.

"Ventricular bigeminy" due to persistent double re-entry with aberrant conduction of the first, and block below the pacemaker of the second re-entrant impulse. Attempt at a third re-entry accounts for the prolongation of the subsequent R-P.

c, Record taken on the afternoon of April 28, 1945.

In addition to instances of single, double, and, attempted triple re-entry as described in *a* and *b*, there is, at the beginning of the tracing, an instance of triple re-entry with conduction to the ventricles of the first and second reciprocal impulses and conduction to the auricles of the third reciprocal impulse (second retrograde P wave). An attempt at a fourth re-entry is indicated by the prolonged R-P of the subsequent nodal beat. Discussed in text.

An attempt at retrograde conduction had to be assumed, after the last discharge of the pacemaker in this group, to explain, as in previous records, the appearance of the re-entry following the subsequent nodal beat. If our interpretation is correct, this is an instance where the re-entrant impulse completes three circuits. Of the three re-entrant impulses, two reach the ventricles whereas the third is blocked below the pacemaker. Of the three retrograde impulses, due to re-entry, only the second reaches the auricles. The last one represents an attempt at a fourth consecutive re-entry.

Fig. 5. (For legend see opposite page.)

Interference of the sinus impulse with the re-entry phenomenon: Digitalis, which was apparently responsible for the conditions in the A-V region necessary for the establishment of re-entry, also had a depressing effect on the sinus node. Block between the sinus and the auricles or marked slowing of the impulse formation in the former was present when the nodal pacemaker dominated. With the disappearance of the digitalis effect, more and more evidence of sinus activity appeared in the tracings, the sinus impulses giving rise to P waves different in contour from those due to retrograde conduction. They appeared at irregular intervals and no time relationship existed among them which would permit a definite diagnosis of sino-auricular block. However, their irregular appearance caused an interesting interplay of the sinus impulses and the retrograde nodal impulses in the activation of the auricles and led in some instances to the appearance of fusion P waves. Furthermore, the time relation of either of these P waves (sinus, retrograde, or fusion) to the nearest ventricular complex had a definite influence on the occurrence of re-entry. This can be seen in Fig. 5 and diagrammatically in Fig. 8. P waves falling 0.16 second or more after a nodal beat did not interfere with the re-entry phenomenon, regardless of whether they were of sinus or A-V nodal origin (Fig. 8,a-c). Therefore, the point of re-entry had to be localized below the auricles, as already postulated in other instances of reciprocal rhythm.[5,13,16,21] It should be re-emphasized that an inverted (retrograde) P wave, "sandwiched" between a bigeminus is not a conditio sine qua non for the diagnosis of a reciprocal beat, provided that evidence for retrograde conduction is present elsewhere in the tracing and that the coupling of the reciprocal beat shows the expected duration.

Sinus impulses, which gave rise to P waves occurring at an interval shorter than 0.16 second before or after a QRS complex, penetrated deeply enough into the conduction system to interfere with the retrograde impulse and its re-entry (Fig. 8,e,f,g). During a period of more rapid rate of the sinus node (Fig. 5, Lead I), sinus impulses reached and discharged the nodal pacemaker before its automatic action and produced normally conducted beats with a P-R of 0.16 second (Fig. 8,h). Those of the sinus impulses which reached the nodal pacemaker while the sinus rate was slower, found the pacemaker already automatically discharged and therefore refractory (Fig. 8,e,f,g).

There was one instance where a sinus P wave falling 0.12 second after the QRS discharged the pacemaker (Fig. 5, Lead I) and was conducted to the

Fig. 5.—Record taken May 20, 1945. Interference between sinus and A-V nodal impulses.

Conventions as in Fig. 3. In addition *S* stands for S-A node, the oblique lines between S and A indicate conduction between sinus node and auricles.

Retrograde P waves as well as sinus P waves are seen. The latter appear at irregular intervals and, on occasion, give rise to fusion P waves identified by their intermediate contour. Note that reciprocal beats, recognized by fixed and short coupling to the preceding nodal beat and by aberrant intraventricular conduction, occur after retrograde P waves as well as after sinus and fusion P waves, indicating that the level of re-entry is within the A-V junction. In Lead I, the auricles are activated by the sinus node with the exception of the third auricular complex which is due to a fusion of sinus and A-V nodal retrograde impulse. Complete A-V dissociation is present in the first part of Lead I. Later the sinus node speeds up and gives rise to a series of four impulses conducted to the ventricles. The first of them shows a prolonged P-R (0.40 second) and slightly aberrant intraventricular conduction. Its coupling to the preceding nodal beat is longer than that of any reciprocal beat throughout the record. The rate of the nodal pacemaker, corresponding to an R-R of 1.00 to 0.04 second, is somewhat faster and the R-P intervals permitting re-entry (0.20 to 0.22 second) are shorter than in previous records. For further discussion see text and Fig. 8.

ventricles.   The ventricular complex showed considerable difference in its contour and time of coupling as compared with instances of re-entry in the same record. Apparently the sinus impulse fell just in time here not only to prevent re-entry of the preceding nodal impulse but also to find the pacemaker after its refractory state (Fig. 8,d).
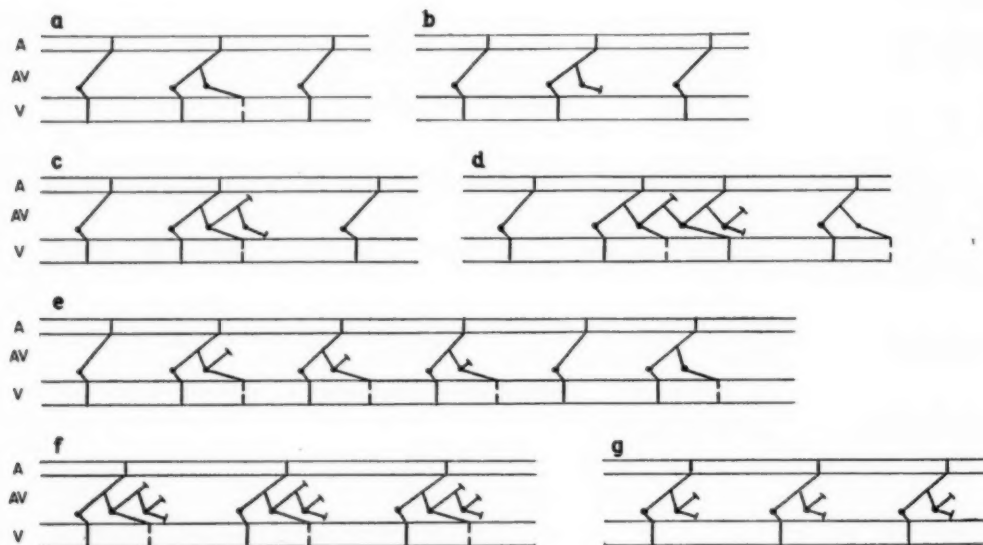

Fig. 6.—Diagrammatic representation of the various forms of re-entry of the nodal impulse as encountered in Fig. 1 to Fig. 4. Conventions as in Fig. 3. a, Re-entry; b, blocked re-entry; c, double re-entry (second blocked); d, multiple re-entry to both ventricles and auricles (the last blocked in both directions); e, varying R-P prolongation due to re-entry with varying second retrograde conduction; f, nodal rhythm with slow rate, long R-P and bigeminy due to double re-entry, the second blocked in both directions; and g, nodal rhythm with slow rate and long R-P due to concealed re-entry (blocked re-entry with blocked second retrograde conduction).

The re-entry time: Although varying slightly (0.48 to 0.58 second) in tracings taken on different days, the coupling of the reciprocal beat to the initiating nodal beat remained constant throughout single records and, indeed, was the only indication of the underlying mechanism in those instances where retrograde conduction did not manifest itself by the appearance of a retrograde P wave. The time of the coupling of the two beats would represent the time of the whole re-entry process, if the conduction time from the pacemaker to the ventricles were the same both for the nodal and the reciprocal impulse.   However, the conduction of the former occurs over fibers which had time to recover from the preceding conduction, whereas the re-entrant impulse which gives rise to the reciprocal beat is conducted over the path below the pacemaker after a much shorter time for recovery.[28]   A state of absolute refractoriness of the path between the nodal pacemaker and the ventricles is responsible for actual blockage of the re-entrant impulse, whereas relative refractoriness of the conducting tissues below the pacemaker causes a prolongation of the time of conduction through the bundle and delay in the right bundle branch system.

In the only instance, already discussed, where conduction of the sinus impulse occurred after an R-P distance of 0.12 second (Fig. 5, Lead I), the coupling of the conducted beat to the preceding automatic beat was longer than any coupling due to re-entry.   This conducted sinus impulse was followed by a series of other conducted sinus beats as a result of increased rate of impulse formation.   The difference (0.24 second) between the P-R of the first sinus beat (0.40
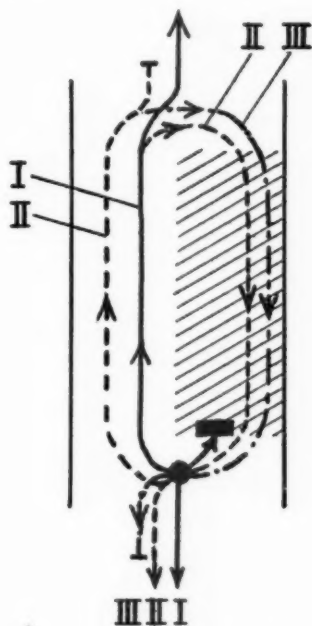

Fig. 7.--Diagrammatic analysis of the spread of the nodal impulse through the depressed region in the A-V junction, the mechanism of re-entry.   The shaded area represents a region of more marked depression in the A-V junction permitting forward conduction but blocked for retrograde conduction as indicated by the short horizontal bar (unidirectional block, monodromia).   An impulse (I, solid line) arising in the A-V nodal pacemaker (solid circle) is conducted down to the ventricles and—in retrograde direction—to the auricles.   The retrograde impulse, having slowly by-passed the region of retrograde block now enters in a forward direction (II, dashed line) the fibers blocked for retrograde conduction and returns to the pacemaker, which had time to recover from its refractory period and may be discharged.   The re-entrant impulse (II) may give rise to a reciprocal beat of the ventricles or may find the region below the nodal pacemaker still refractory (blocked re-entry).   While re-entry to the ventricles is attempted or completed, the re-entrant impulse (II) may again penetrate into the fibers permitting retrograde conduction and start a second circuit leading, if completed (III, dot-dash line), to a second discharge of the nodal pacemaker and to a second reciprocal beat or block below the pacemaker (as indicated in the diagram).   Thus, a circulating movement within the A-V junction may be initiated.

second) and that of the second sinus beat (0.16 second), which must be identical with the shortening of the R-R interval between the first two sinus beats (0.96 to 0.72 second), indicates the delay in transmission of the impulse on its way from the nodal pacemaker to the ventricles.   A similar state of refractoriness of the path below the nodal pacemaker can be assumed in the case of short coupling due to re-entry of nodal impulses.   Consequently, at least 0.24 second of the coupling of the reciprocal beat may be assumed to be needed for the transmission of the re-entrant impulse from the pacemaker to the ventricles.   The time

needed for conduction of a single re-entry from pacemaker back to pacemaker
was calculated before to be about 0.30 second. This figure plus the time of
0.24 second spent in transmission of the impulse from the pacemaker to the ven-
tricles, as calculated heretofore, corresponds to the average coupling of 0.54 second
found in the majority of the reciprocal beats. However, some error in these
calculations should be pointed out. A sinus impulse approaching the node may
find partially refractory tissue also in a region just above the nodal pacemaker
and below the area of unidirectional block. Therefore, not all the delay of the
slowly conducted sinus beat must necessarily be ascribed to block below the nodal
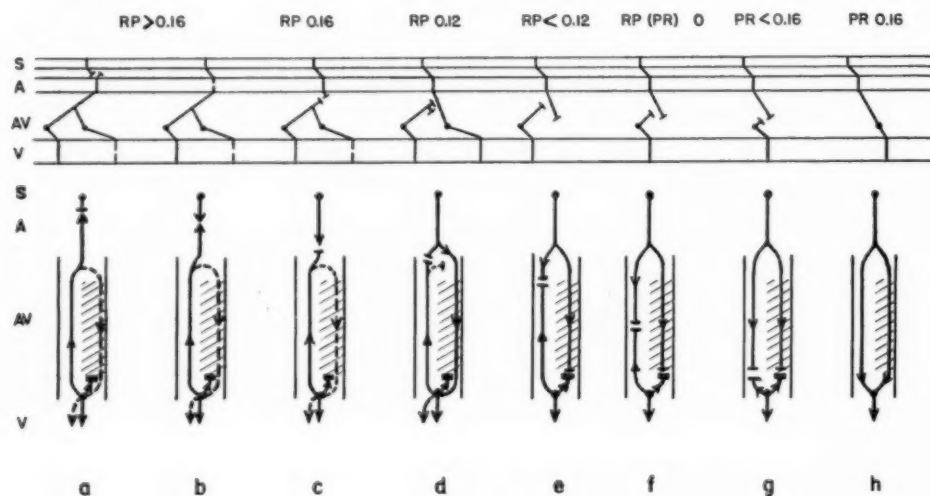pacemaker.

Fig. 8.—Diagrammatic representation of interference between sinus impulse and retrograde nodal
impulse as encountered in Fig. 5. Conventions as in Fig. 5 and Fig. 7. A sinus impulse, giving rise to
a P wave falling 0.16 second or more after a nodal beat, meets the retrograde impulse above the level of
re-entry and does not interfere with the re-entry (a, b, and c). Thus, the reciprocal beat may be pre-
ceded by a retrograde P wave, a sinus P wave or a fusion P wave. Sinus impulses responsible for the
inscription of a P wave less than 0.12 second after or less than 0.16 second before the nodal beat pene-
trate deep enough into the A-V junction to prevent re-entry (e, f, and g). However, they fail to discharge
the nodal pacemaker which remains refractory or becomes so after its spontaneous discharge (f repre-
sents conditions where R-P and P-R are close to zero). A sinus impulse giving rise to a P wave 0.12
second after the QRS arrives at the critical level of the A-V junction just in time to prevent re-entry
and to reach the pacemaker outside its refractory state and, therefore, is conducted to the ventricles (d).
When the sinus node speeds up, an impulse giving rise to a sinus P wave late in diastole discharges the
pacemaker and is conducted to the ventricles with a P-R of 0.16 second (h).

When re-entry occurs, the *time of retrograde conduction* from the nodal pace-
maker to the point of re-entry is not identical with the R-P interval of the nodal
beat since re-entry takes place below the auricles. Actually, the R-P is a)
longer by the time the impulse requires to be conducted from the point of re-entry
to the auricles and b) shorter by the time the impulse requires to travel from its
point of origin to the ventricles. As the latter can be assumed to be constant for
all instances where a nodal discharge occurred after a longer pause, i.e., in all
instances of automatic nodal beats, the R-P interval remains an indicator of the
speed of retrograde conduction, and the critical value of R-P prolongation neces-

sary for the occurrence of re-entry corresponds to the critical value of the conduction time up to the level of re-entry.   In one record (Fig. 5), it was possible to compare the duration of forward and retrograde conduction. Whereas the shortest forward conduction (0.16 second) was well within normal limits, the shortest retrograde conduction was 0.18 second and re-entry occurred only after prolongation of R-P to 0.22 second.

In short, the following statements can be made: The most constant sign of reciprocal beating during nodal rhythm is the fixed coupling of the reciprocal beat. This coupling consists of a) the time for retrograde conduction from the pacemaker to the point of re-entry, b) the time for forward conduction from the point of re-entry to the pacemaker, and c) the time for forward conduction of the reciprocal beat from the nodal pacemaker to the ventricles minus the corresponding time for the nodal impulse which gives rise to this re-entry.   For the case presented, the time for the sum (a + b) was calculated to be about 0.30 second and that for c) to be 0.24 second, giving a total of 0.54 second, which is in close accord with the values obtained by actual measurements of the coupling of the reciprocal beats.   An inverse relationship was found between a) and (b + c).   This is shown by the fact that in one instance of successive re-entry the coupling remained fixed, although the respective R-P intervals indicated progressive shortening of the retrograde conduction (Fig. 3,a)

Clinical implications: The existence of a circulating movement of the impulse in the heart has been proved only in animal experiments.   For the human heart it remains questionable.   It is rejected as the underlying mechanism of different forms of rapid heart action by some authors and accepted by others. "Especially for nodal tachycardia with retrograde P waves the idea of continuous reciprocal rhythm can be entertained."[29]   For the present, there is no more reliable method to prove or disprove the existence of such a mechanism in the human heart than careful analysis of such clinical electrocardiographic tracings as the ones analyzed in this report.   In this respect, the case presented here may be a positive contribution to the unsolved problem.

<div align="center">SUMMARY AND CONCLUSIONS</div>

1.   Observations are reported on the electrocardiograms of a patient with arteriosclerotic heart disease in whom digitalization was followed by persistent nodal rhythm with delayed retrograde conduction and re-entry within the A-V node (recorded in 610 instances).

2.   Evidence is presented for the occurrence of repetitive re-entry with instances of two retrograde P waves and two reciprocal beats in succession.   Evidence of re-entry with block of the impulse below the nodal pacemaker and evidence of attempted re-entry with block within the re-entry path are also given.

3.   An approximate estimate of the re-entry time (0.30 second) was obtained by comparing the R-R interval of two consecutive nodal beats with that of two nodal beats containing a reciprocal beat or a blocked reciprocal impulse.   Peculiar circumstances permitted the calculation of the delay (0.24 second) in conduction time of the re-entrant impulse on its way from the nodal pacemaker to the

ventricles.   The sum of these two values (0.54 second) was in agreement with the actually measured average value of the coupling of the reciprocal beats.

4.   In records where both the sinus and A-V node were active, most sinus impulses giving rise to sinus P waves failed to interfere with re-entry of the retrograde impulse.   This fact confirms previous observations indicating that re-entry may occur below the auricles and again demonstrates that a reciprocal beat may be preceded by a sinus P wave.

5.   In a case of nodal rhythm with "premature beats," fixed coupling and evidence of delayed retrograde conduction permit the distinction between reciprocal beating and A-V dissociation with ventricular captures.

6.   The occurrence of repetitive re-entry is, for the present, the only clear evidence of the existence of a circulating movement of the impulse within the human heart.

The authors are indebted to Dr. L. N. Katz for his valuable criticism and suggestions.

ADDENDUM

While this article was in preparation, a strikingly similar case was observed and similar conclusions were arrived at in Affula, Israel by Dr. Peter Fleischmann, who is publishing his observations under the title "The Latent and Manifest Reciprocating Mechanism in Lower A-V Nodal Rhythm Coexistent With Sinoauricular Rhythm." We are indebted to Dr. Fleischmann for the opportunity to study his material which fortifies the analysis presented in this paper.

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NORMAL UNIPOLAR VARIANTS WITH SPECIAL REFERENCE TO THE Q AND T WAVES

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SINCE their introduction by Wilson and his associates,[1-4] unipolar leads have been quite widely used. A still confusing question is the extent and degree of the normal variations in this system of leads. Although this matter has been studied considerably there is still need for further evaluation of normal T wave and Q wave patterns particularly in the unipolar limb leads. We wish to report some of our observations and to propose a simple classification which we have found to be helpful.

Wilson and his associates clarified the subject by pointing out that the QRS-T complex of a given unipolar limb lead (V_R, V_L, or V_F) frequently, but not invariably, resembles the QRS-T complex obtained in one of the customary precordial leads. They showed that this relationship varied, depending on the position of the heart in the chest. They described five cardiac positions, ranging from vertical, manifested by a pattern in Lead V_L resembling that of V_1 and V_2 and a pattern in Lead V_F like that of V_5 and V_6, to horizontal, shown by a QRS complex in Lead V_L like that in V_5 and V_6 and in V_F like that in V_1 and V_2. They also included a sixth, and indeterminate position, in which no obvious relationship existed.

Goldberger[5] modified the Wilson procedure in obtaining unipolar limb leads by removing the connection of the central terminal from the limb to which the exploring electrode was attached. Tracings obtained thus with 5,000 ohms resistance in each of the connections of the indifferent electrodes are identical in contour, but 50 per cent greater in voltage than those recorded by the Wilson technique. Goldberger has described the commoner patterns in his augmented unipolar limb leads aV_R, aV_L, and aV_F,[6,7] and has commented upon their relationship to the patterns in semidirect precordial and esophogeal leads.[8,9] Myers and Klein,[10] to elucidate further the relationship between semidirect and unipolar extremity leads, undertook a study of normal subjects, using multiple semidirect leads and augmented unipolar limb leads. They found that the counterpart of the QRS-T pattern of each of the unipolar limb leads could be demonstrated in a precordial or esophageal lead. The findings in Lead aV_L were classified into five patterns: (1) QRS-T resembling that of Leads V_5 and V_6, (2) QRS-T resembling that of V_1 and V_2, (3) QRS-T resembling that of the transitional zone

(generally Lead V_3), (4) QRS-T resembling an esophageal lead opposite the posterior aspect of left ventricle, (5) QRS-T resembling esophageal leads taken from behind or above the left atrium. The findings in Lead aV_F were classified into four patterns: (1) QRS-T resembling the pattern in Leads V_1 and V_2, (2) QRS-T resembling that of the transitional zone. (3) QRS-T resembling that of Leads V_5 and V_6, (4) QRS-T resembling an esophageal lead opposite the posterobasal aspect of the left ventricle.

METHODS OF STUDY

We have been able to reproduce many of the various normal patterns of the unipolar limb leads in a single subject by having the subject lie in various positions and by varying the position of the heart by deep inspiration and expiration. The production of many patterns in a single subject considerably clarifies the relationship of various patterns to the position of the heart. We have paid considerable attention to the Q and T waves, for these are the most confusing with respect to normal types. Over 200 tracings of subjects known to be free of cardiovascular disease were reviewed. The customary Wilson precordial leads and augmented unipolar limb leads were taken. Those patients who were able to stand were studied by fluoroscopy and the anatomical position of the heart determined.

FINDINGS

I. *Q Wave Patterns*

  1. *In Lead aV_L.—*

  A. *Septal Q:* Often a small Q was found which was due to the initial impulse spreading from left to right through the septum.[11] This is shown in Fig. 1. A Q wave of this origin is very narrow, being less than 0.04 second in width and not very deep.

  B. *Endocardial or Cavity Q:* We wish to point out three observations: (a) We were able to produce all types of cavity Q waves found normally in Lead aV_L in the same subject. The patterns thus produced concur with types shown by Myers.[10] (b) A Q wave preceded by an inverted P wave is usually considered to be a normal pattern in a vertical heart.[9,10,12] This is true provided the Q wave is less than 0.04 second in width. However, infarction can occur in a vertical heart. In spite of a preceding inverted P wave the Q wave in aV_L may be significant, and the significance is shown by the fact that the Q is wide and slurred. This point will be discussed later. (c) The width of the Q and not the depth is most important in separating normal from abnormal Q waves. If the width is over 0.04 second and the wave is slurred, myocardial infarction should be suspected no matter what the depth of the Q wave is.

  It has been shown that in a vertical heart the Q wave may vary from a small deflection to a QS pattern. The potentials from the left atrium and the cavity of the left ventricle (through the mitral orifice) are referred to the left arm. The depth of the Q and height of the R depend on the position of the apex. If the apex is forward then Lead aV_L looks directly into the left atrium and a deep Q is found followed by a small R produced by the posterobasal aspect of the left ventricle.

This pattern may be produced by making the apex go forward by having a subject inspire deeply or assume the supine position. As the apex is made to go backward, by having the patient assume a sitting position, then the Q wave becomes decreased and the R wave becomes larger because now the electrode faces less cavity potential and more of the posterobasal aspect of the left ventricle. Such Q waves are never over 0.04 second in width. In Fig. 2 are shown the various types of the Q waves found normally in Lead aV$_L$. These were all produced in the same individual by various maneuvers. It can be seen that when forward flexion was applied with the subject in the sitting position, the apex was forced very far back and Lead aV$_L$ revealed a large R wave and a very small Q wave. As the patient changed from a seated to a supine position the Q became deeper because the apex was moved forward and so aV$_L$ faced cavity potentials. It also may be noted that during inspiration, regardless of the position of the subjects, the diaphragm moved down and the apex moved forward; thus aV$_L$ again faced cavity potentials and therefore recorded a deep Q wave.
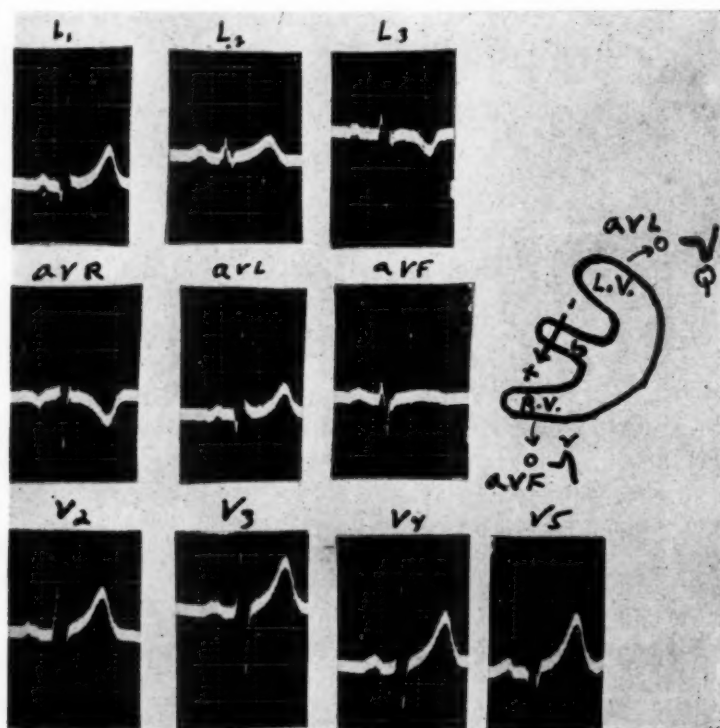

Fig. 1.—Septal Q in aV$_L$ and left precordial leads. Note Q wave in aV$_L$ and V$_5$ due to the spread of the stimulus through the septum from left to right away from the electode, as is shown schematically. Also note the flat T in aV$_F$ preceeded by an R less than 5 mm. in height.

2.   *In Lead aV$_F$.—*

A.   *Septal Q:*   This is usually seen in a very vertical heart and is produced by the impulse spreading from left to right through the septum and therefore moving away from the aV$_F$ electrode. This is shown in Fig. 3.
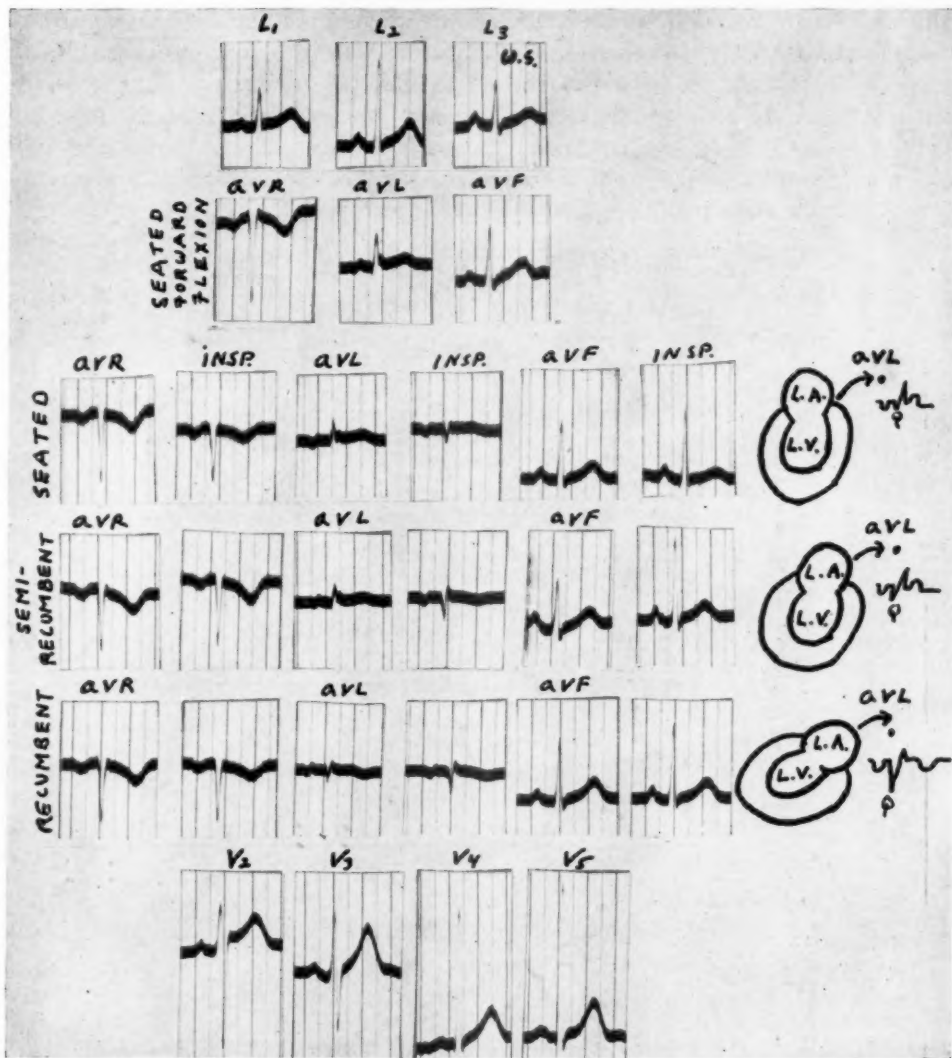
Fig. 2.—Endocardial or cavity Q waves in aV$_L$. Note that the Q wave increased as the subject moved from the seated to the recumbent positions since the apex goes forward. In the recumbent position and also during deep inspiration a QS pattern is produced because the electrode lies over the left atrium. This is shown schematically. Note: *INSP.* = inspiration.

B. *QS Pattern:* This configuration is seen often in very horizontal hearts in which aV$_F$ does not pick up the initial positive wave through the septum because the axis of the exploring electrode of this lead lies perpendicular to it. Under these circumstances, Lead aV$_F$ faces the right ventricle and is controlled entirely by the greater negativity created by the outward passage of the impulse through the left ventricular wall which overcomes the small positive influence of the passage of the impulse through the thin right ventricular wall. This is shown in Fig. 4,

which is the tracing of an obese male who had no signs or symptoms of cardio-vascular disease. By fluoroscopy his heart was found to be in a transverse posi-tion. When he assumed the recumbent position Lead aV$_F$ showed a small R because its exploring electrode faced the initial positive impulse of the septum. This was also seen in Fig. 1. However, when the subject was seated the axis of Lead aV$_F$ apparently became perpendicular to the septal impulse and so did not register its potentials and showed only a QS pattern.
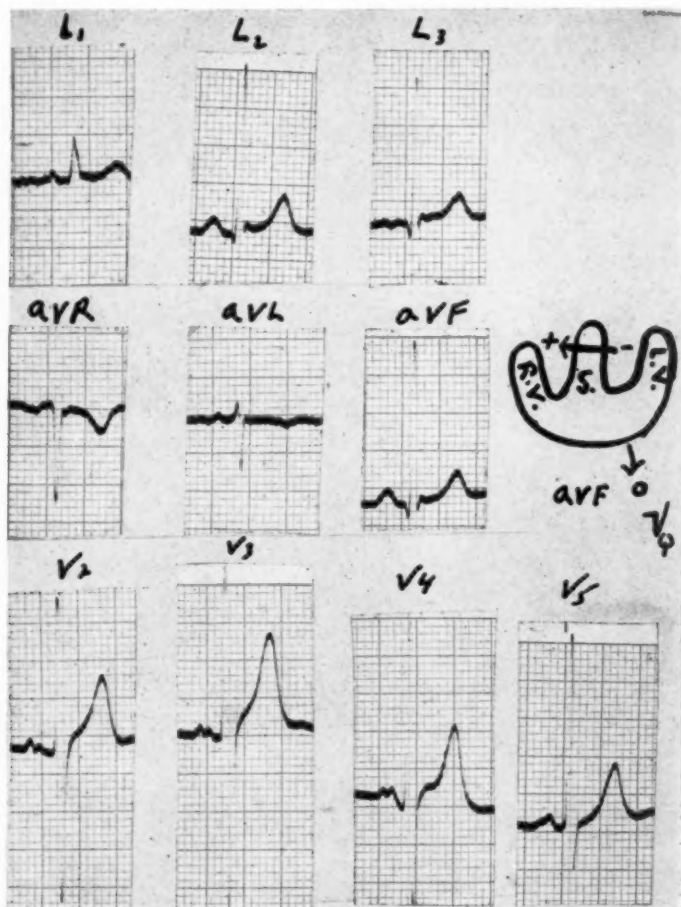

Fig. 3.—Septal Q in aV$_F$. Note Q in aV$_F$ due to spread of stimulus through the septum from left to right away from the electrode as is shown schematically. Also note the inverted T in aV$_L$ preceeded by an R less than 5 mm. in height.

C. *Cavity Q:* In a vertical heart with clockwise rather than the usual counterclockwise rotation on its longitudinal axis, the apex is displaced forward. The depth of the Q wave depends on the amount of cavity potential the electrode faces, since this Q is produced because the left leg lead faces the atrioventricular groove and posterobasal aspect of left ventricle. In these cases the Q may be decreased by having the patient assume a recumbent position and thus allow the

apex to fall backward somewhat.   The electrode then no longer faces the atrio-
ventricular groove, but faces only the wall of the left ventricle.   This is shown in
Fig. 5, which is the tracing of a 25-year-old man of medium build who was free
of signs and symptoms of cardiovascular disease.   By fluoroscopy his heart was
found to be in a vertical position.   In this case it can be told that the apex is
forward because in the chest leads the height of the R wave suddenly decreases
from the V_4 to the V_5 position.   When the patient is seated, aV_F shows a Q
wave because its electrode is facing cavity potential.   A large R follows which is
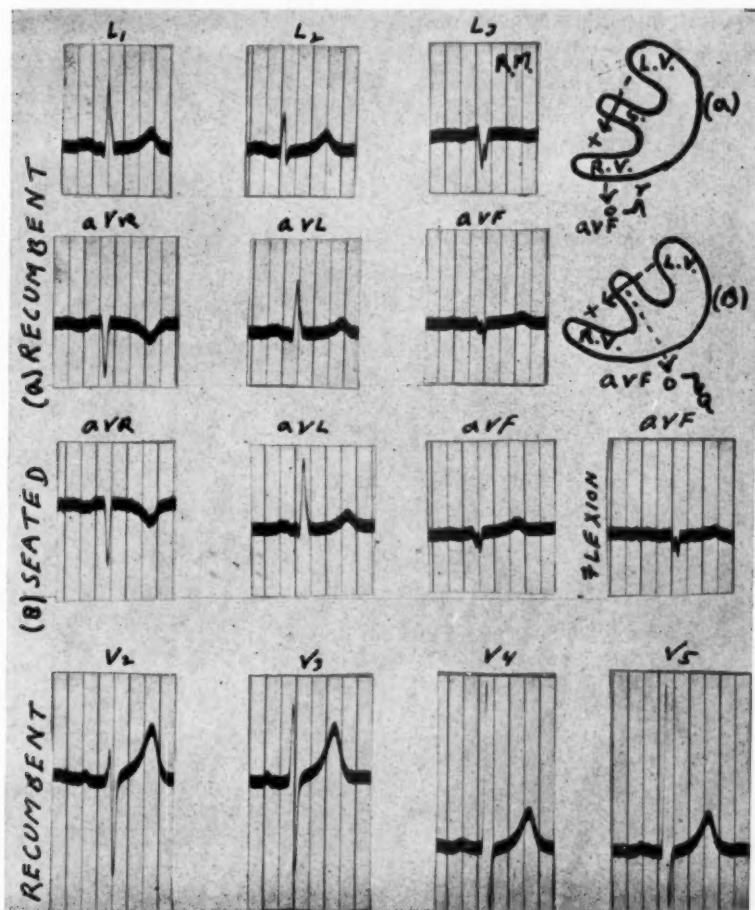

Fig. 4.—QS pattern in aV_F.   Note small R in aV_F in the (A) recumbent position due to septal
impulse going toward the electrode.   In (B) seated position, a QS appeared in aV_F because now the
electrode is perpendicular to the septal inpulse and so did not record its wave.   These are shown sche-
matically.

produced by the posterobasal aspect of the left ventricle.   When the subject
assumes the recumbent position the apex is still forward but it has moved back
somewhat because now the Q has decreased to half its depth and the left leg only
faces the left ventricular surface and no cavity potential.   The small Q still present
is due to the initial septal impulse going away from the electrode.
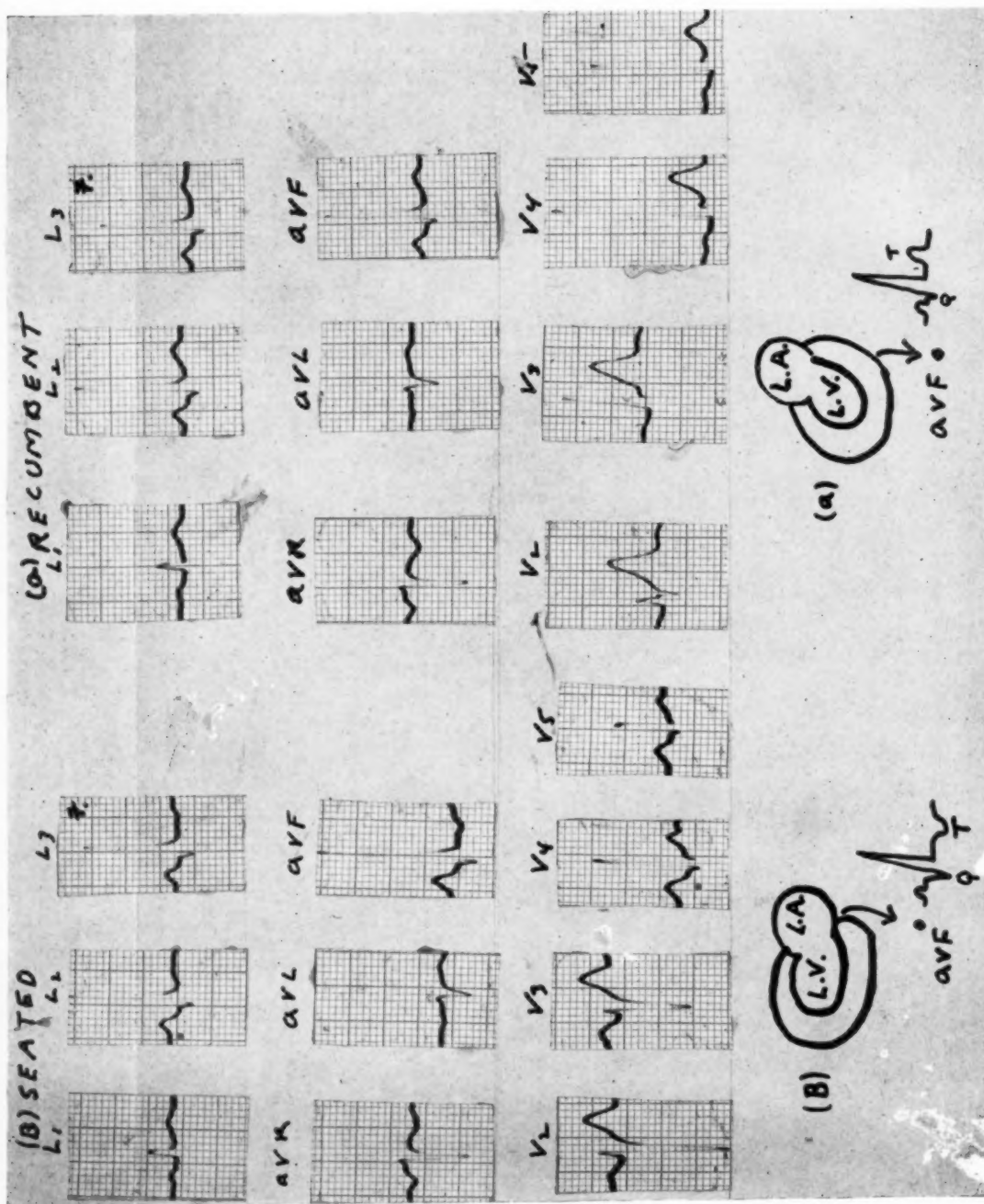
Fig. 5.—Cavity Q wave in aV$_F$. Note Q wave in aV$_F$ when the subject assumes the (B) seated position due to apex being forward and the electrode facing the atrioventricular groove. In the (A) recumbent position the apex goes backward and the electrode is no longer facing the atrioventricular groove, as is shown schematically. Note the decrease in height of the R wave from V$_4$ to V$_5$ positions indicating that the apex is forward. Also note the inverted T in the seated position even though the R is more than 5 mm. in height. In the recumbent position the T wave becomes upright when the cavity potential is eliminated.

3. *In Lead aV_R.—*

A. *QS Pattern:* This lead usually shows a QS pattern (Figs. 1, 2, 3, and 4) because it faces the base of the heart and thus the cavity potentials of both right and left ventricle are recorded. At times a small R may be present, due to the initial septal impulse, as is shown in Fig. 5.
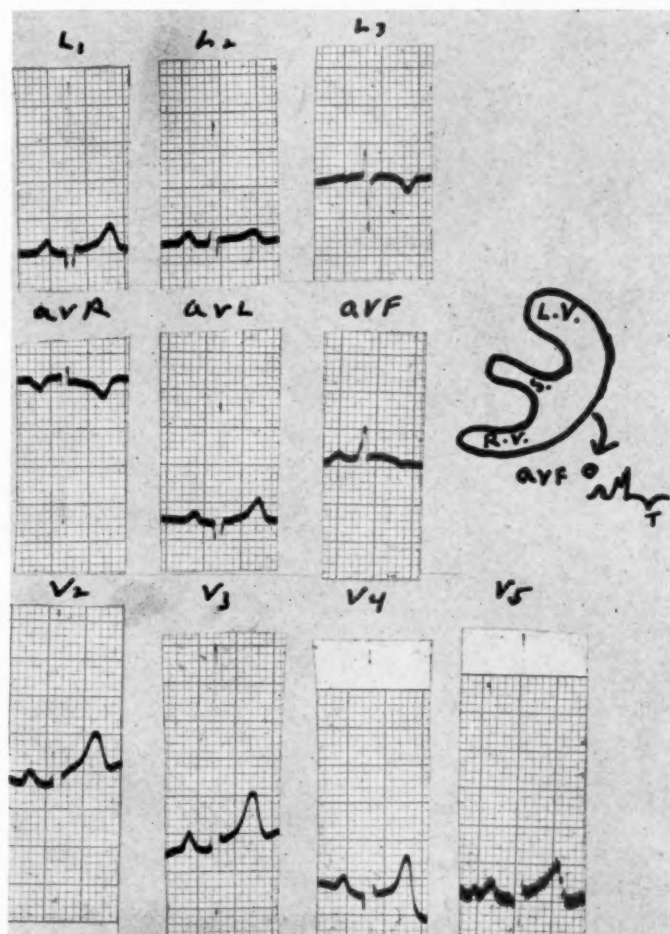
Fig. 6.—Septal T wave. Note that the T is inverted in aV_F when the electrode is facing the septal area as is shown schematically.

4. *Precordial Semidirect Leads.—*

A. *Septal Q:* This is seen in left ventricular leads and corresponds to the Q seen in Lead aV_L in these cases. Fig. 1 reveals this type of Q in Lead V$_5$.

B. *QS Pattern:* This configuration often is found in leads taken over the right ventricle in horizontal hearts because the axes of the exploring electrodes of these leads lie perpendicular to the initial septal impulse and so do not record it. Under these circumstances these leads are controlled by the greater negativity created by the outward passage of the impulse through the left ventricular wall.

C. *Deep Q Waves in Left Ventricular Leads in Children:* These Q waves have never been explained but may be due to the greater thickness of the septum in children and therefore the septal impulse which moves away from the left ventricular leads may produce a deeper Q wave than the septal Q seen in adults.

II. *T Wave Pattern*

  1. *In Leads aV_L and aV_F.—*

  A. *The T Waves:* The T waves are usually upright in these leads. However, if the R is less than 5 mm. in height the T wave may be upright, inverted, or flat according to Sokolow and Friedlander.[13] In Fig. 1 is shown a flat T in Lead aV_F where the R is only 2 mm. in height. The heart in this case was shown to be in a horizontal position by fluoroscopy and by the presence of a large R in Lead aV_L. An inverted T is seen in aV_L in Fig. 3 where the R is only 2 mm. The heart in this case is in a vertical position. We have also found this to be true in our cases, except when Leads aV_L or aV_F are facing cavity potentials and so have Q waves initially. In these cases no matter how large the R, the T may be flat or inverted. This is shown in Fig. 5. When the subject was seated, aV_F showed a Q followed by a large R (greater than 5 mm.) and the T wave was inverted. When the patient assumed the recumbent position, the cavity potential was eliminated and the T wave became upright. This is not true in cases where the initial Q is the result of septal activation.

  B. *Transitional or Septal Zone T Waves:* If Leads aV_L or aV_F face the transitional zone of the heart the T wave may be flat or inverted normally. This is shown in Lead aV_F of Fig. 6, which is the tracing of a young man free of cardiovascular disease.

  2. *In Lead aV_R.—*

  A. *The T Waves:* Normally aV_R never has an upright T wave. If upright then disease is definitely present. However, an inverted T wave does not exclude disease for damage may be present. In all our figures so far discussed the T waves of Lead aV_R are normally inverted.

  3. *Precordial Indirect Leads.—*

  A. *The T Waves:* Usually the T waves are upright except that they may be inverted in right precordial leads in children.

<div align="center">DISCUSSION</div>

Inverted P in aV_L With Infarction: As we have seen Q waves may be present normally but they are never wider than 0.04 second and seldom slurred. If wider than 0.04 second then this is indicative of an infarction. An inverted P wave preceding a Q wave does not exclude disease. We have seen myocardial infarcts revealed in aV_L by a wide Q (0.04 second or more) and preceded by an inverted P. An inverted P wave simply means that the exploring electrode is not facing the wave of impulse as it spreads from the sinoauricular node. This is usually the case in Lead aV_L in vertical hearts, but may be seen in semivertical and horizontal hearts. In these cases, if the ventricular surface which aV_L faces becomes infarcted, then the P is still inverted, but is followed by a wide slurred Q measuring 0.04 second or more. The amount and portion of the left ventricular
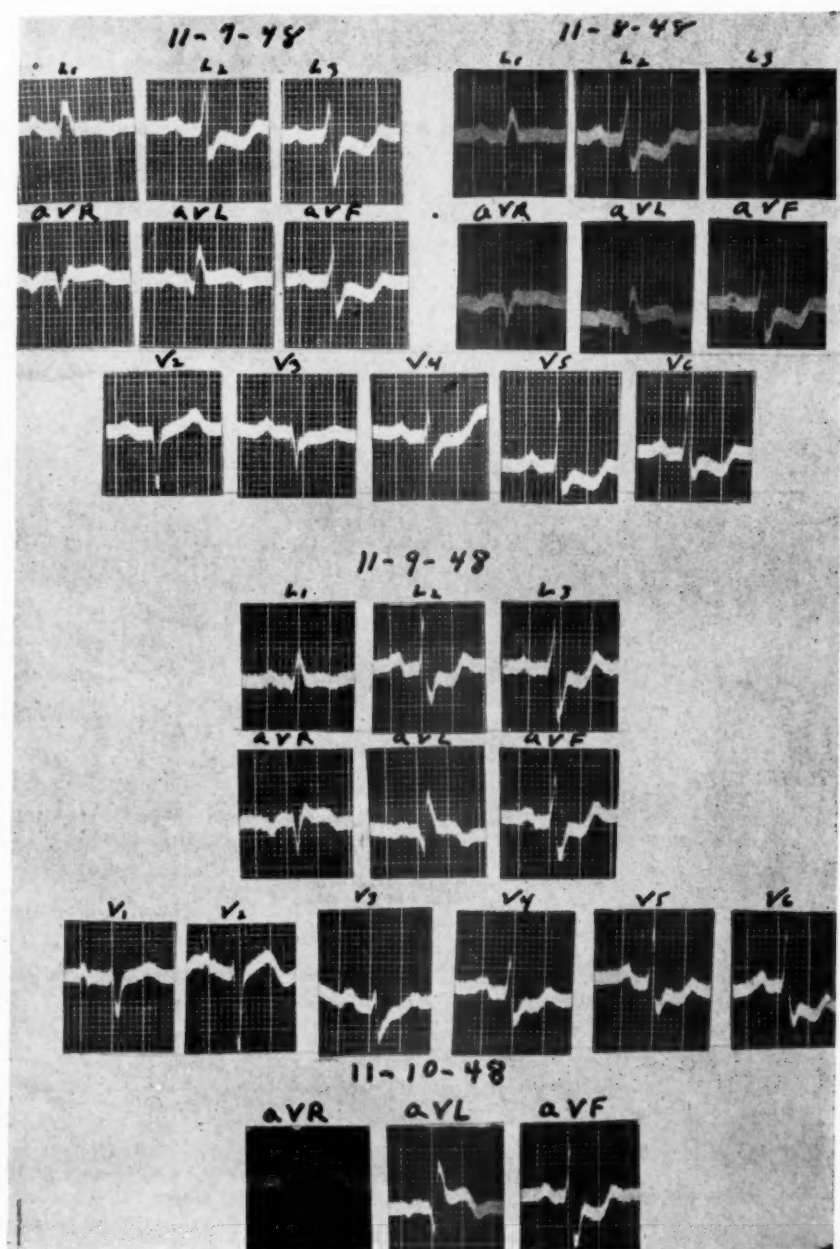
Fig. 7.—Lateral myocardial infarction.   Note that the Q in aV L is wider than 0.04 second and that the P wave is biphasic on Nov. 7, 1948, and Nov. 8, 1948 and actually inverted on Nov. the 9th and 10th.

surface facing aV$_L$ depends considerably on whether the apex is forward or backward, especially in vertical hearts.

In Figs. 7 and 8 are shown tracings taken from two patients who had typical histories of a myocardial infarction. In Fig. 7 of the first patient a lateral myocardial infarction is shown in the first tracing taken on Nov. 7, 1948 by the slurred and wide Q in Lead aV$_L$ with S-T elevation, and by the S-T depression in the chest leads. Serial tracings of Nov. 8, 9, and 10, 1948 showed that the T wave became coved in Lead aV$_L$ and the S-T depression became less in the chest leads.
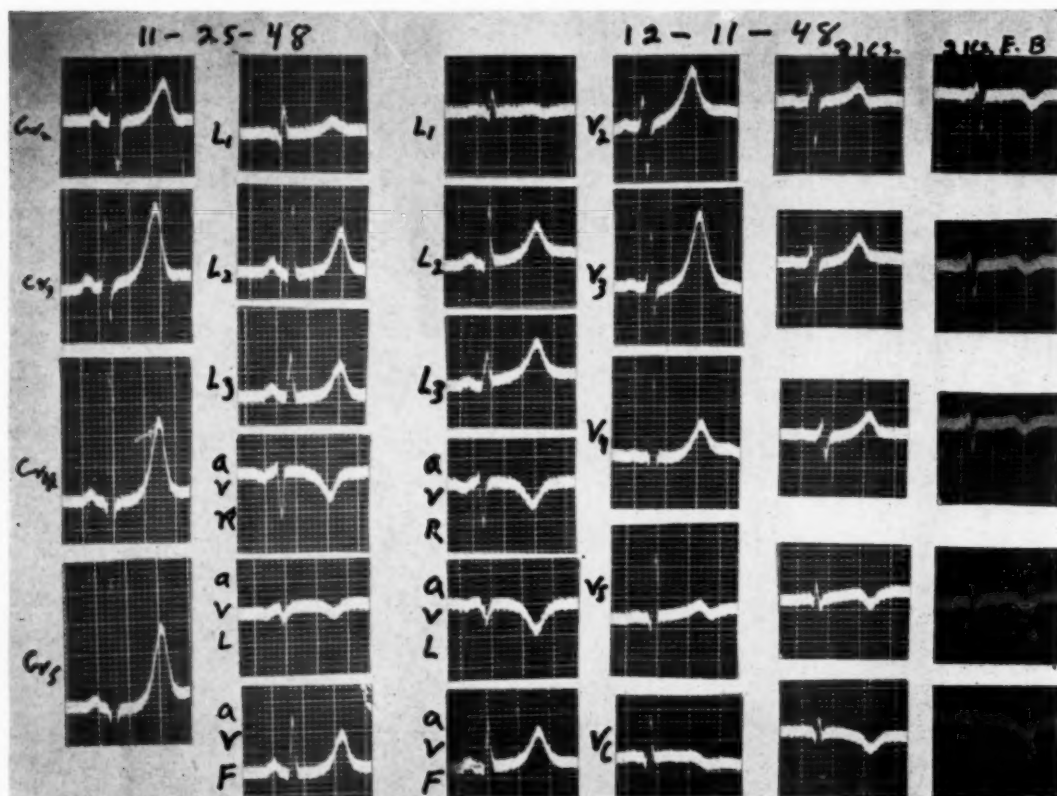
Fig. 8.—High lateral infarction. Note wide slurred Q in aV$_L$ preceded by an inverted P wave. Also note high V$_6$ lead taken in the second and third interspaces on Dec. 11 which is similar to aV$_L$. Note: 3ics = third intercostal space. 2ics = second intercostal space.

It may also be noted that the P wave is biphasic in the tracings of Nov. 7 and 8, 1948 and is actually inverted in the tracings of Nov. 9 and 10, 1948 and in each case is followed by a Q wave which is slurred and wider than 0.04 second. In Fig. 8 of the second patient is seen evidence of a high lateral infarct. Lead aV$_L$ on Nov. 25, 1948 shows an inverted P followed by slurred QS configuration and T wave inversion. On Dec. 11, 1948, it is noted that the T wave has become coved in this lead and has also become inverted in Leads V$_5$ and V$_6$. Higher chest leads in the anterior axillary line in the second and third intercostal spaces reveal a pattern similar to aV$_L$, confirming the diagnosis of a high lateral infarction.

In Fig. 9 the tracings of a 69-year-old, white man are seen.   He was admitted
to the hospital on May 14, 1947 because of severe dyspnea and ankle edema of
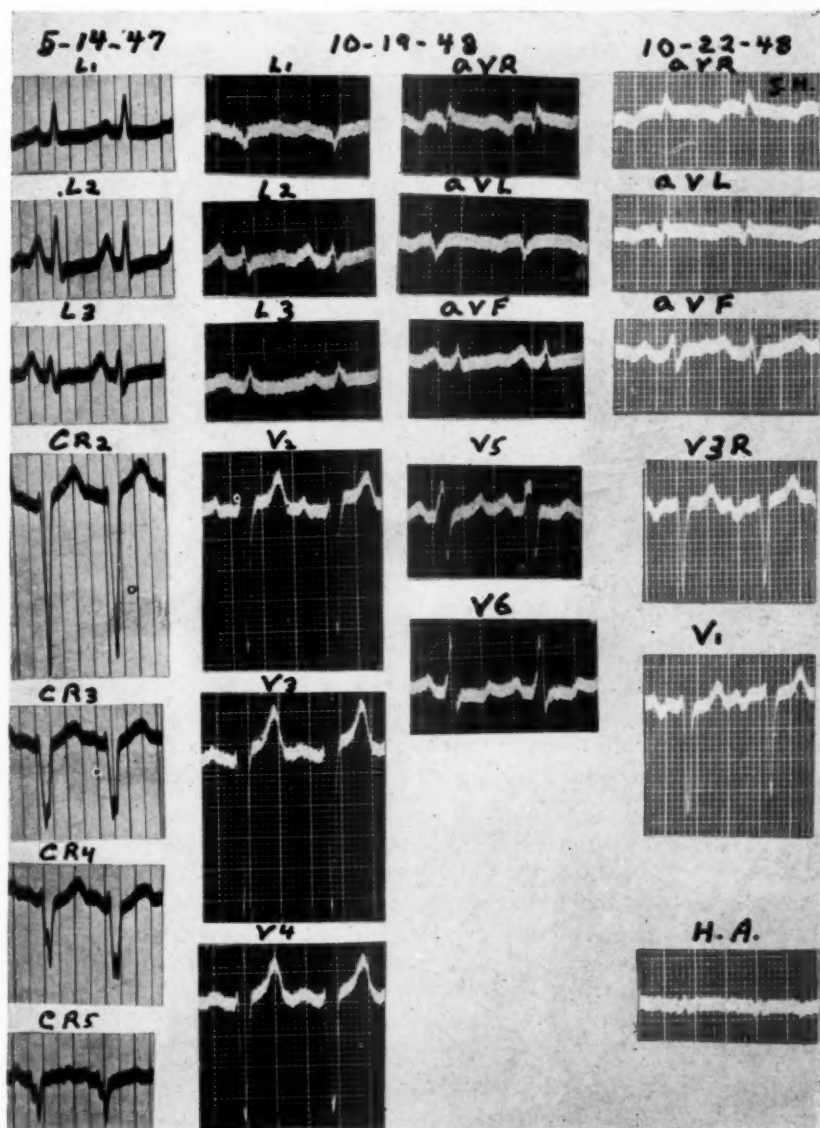
Fig. 9.—Lateral myocardial infarction.   Note wide slurred Q in aV$_L$ preceded by an inverted P
wave.   Also note the change in Lead I on Oct. 19, 1948 as compared to May 14, 1947.   In the pre-
cordial leads are seen small R waves.   On Oct. 22, 1948 a high midaxillary lead is shown which was
similar to aV$_L$.   Note: H.A. = High axillary lead.

several months duration.   An electrocardiogram taken on May 14, 1947 shows
high P waves in Leads II and III and small R waves in all of the precordial leads.
These findings were considered to be compatible with a diagnosis of cor pulmonale.

There was no evidence of an acute myocardial infarction. The following day he developed auricular flutter and was given digitalis. On May 18, 1947, the rhythm was converted to normal and the tracing was similar to that of May 14, 1947, except for some S-T depression which was probably due to the digitalis. He was discharged on June 17, 1947, after several tracing showed no change. An X-ray taken on May 23, 1947, showed an enlarged heart with left ventricular hypertrophy and some emphysema. He was readmitted to the hospital on Oct. 19, 1948, because of an attack of dyspnea and anorexia two weeks before, followed by profound weakness which he could not overcome. An electrocardiogram taken on Oct. 19, 1948 no longer revealed the R wave that was seen in Lead I on May 14, 1947, but now showed a QS configuration in this lead. Lead aV_L shows a wide slurred QS pattern which is preceded by an inverted P wave. The precordial leads have low R waves with some S-T depression in CR_6. Because of the wide slurred Q wave in Lead aV_L, even though preceded by an inverted P wave, it was thought that the patient had a lateral myocardial infarction. In order to rule out right ventricular hypertrophy on Oct. 22, 1948, special leads over the right precordium were taken. Lead V_{3R} (taken on the right side of the chest corresponding to the location of V_3 on the left side) and Lead V_1 did not show any delay in intrinsic deflection or inverted T waves. High chest leads were also taken in order to localize the infarction. Only the high midaxillary lead showed a pattern similar to that of Leads I and aV_L. Two days later the patient expired.

The pathological findings follow. The heart weighed 700 grams as the result of left ventricular hypertrophy. The appearance was that of a hypertensive heart. There was a healed transmural anterolateral infarction of the left ventricle extending to the apex at which point the wall was very thin. The infarction followed the distribution of the anterior descending branch of the left coronary artery and an organized mural thrombus was present. Microscopically the infarction was composed of fibrous tissue. However, in certain spots there appeared some activity.

In retrospect we can understand why the chest leads did not reveal a myocardial window, even though the infarct was anterolateral, since these leads faced the right ventricular area which was anterior because the heart had rotated counterclockwise on its longitudinal axis and tilted posterior on its transverse axis; this resulted in the apex being moved backward. Under these circumstances Leads I and aV_L were the only leads which faced the left ventricle and so revealed the infarct. The large P waves present in Leads II and III on several occasions were probably due to the dilated auricles, since pathologically there was no sign of cor pulmonale.

In these three cases it has been noted that Lead aV_L revealed the signs of an infarction characterized by wide and slurred Q waves and by T wave changes, even though the P waves were inverted.

Importance of the Width of Q Wave in aV_L and aV_F: Goldberger[9] found that if the Q of the left arm lead has an amplitude greater than 30 per cent of the entire QRS complex and has a width of 0.04 second or more and is associated with an inverted T, then an anterior infarct is present. If this pattern is due to a vertical heart, the P is usually inverted, a finding which does not occur with an infarct.
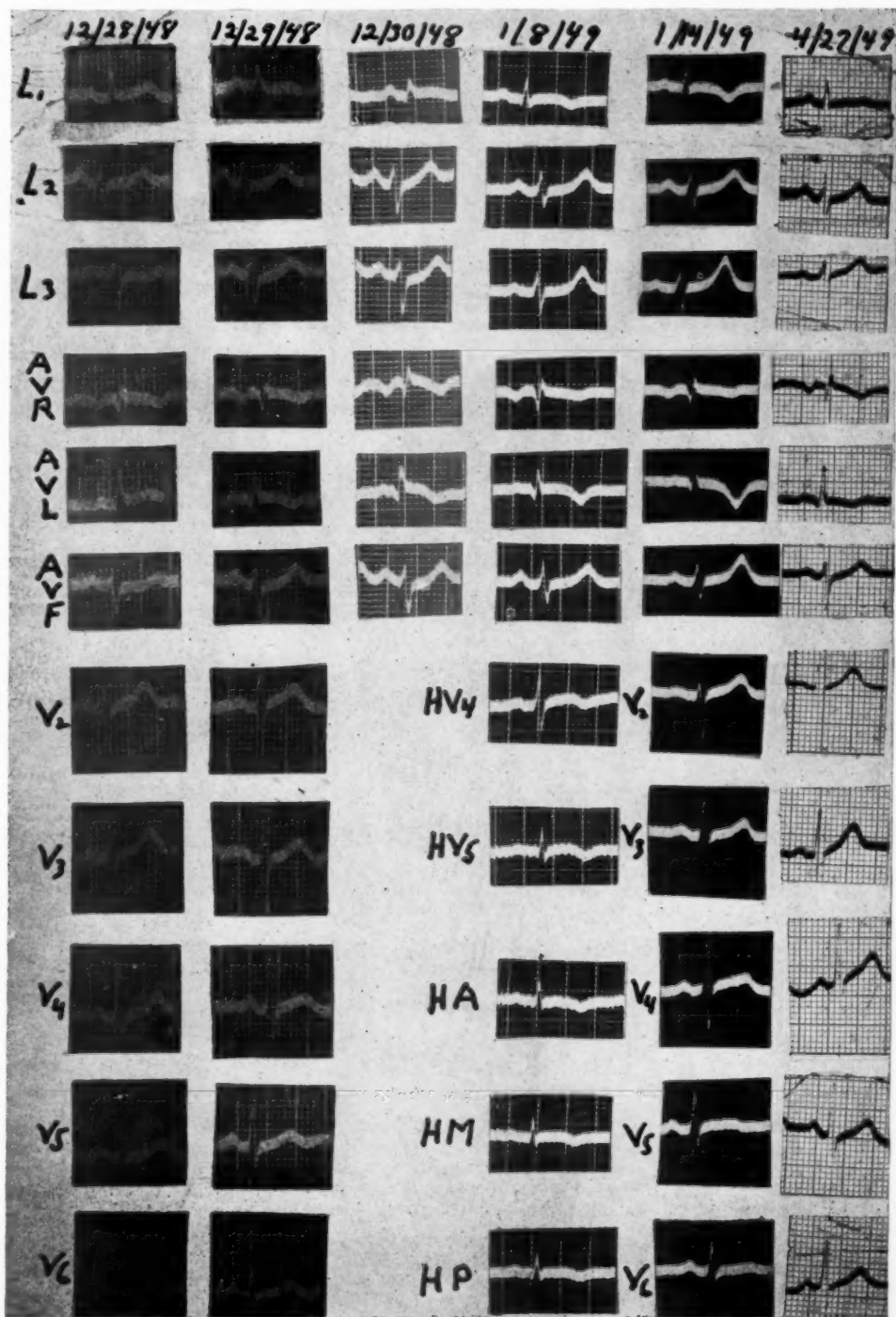
Fig. 10.—High-lateral infarction. Note wide, thick Q in aV_L of 0.04 second duration but not very deep, and serial changes of ST-T segment in this lead. Other leads are normal. Note: HV_4 and HV_5 = Lead two inches above V_4 and V_5. HA, HP and HM = High anterior, posterior, and mid-axillary leads.

In the left leg lead, if the Q wave is 40 per cent of the total amplitude of QRS and wider than 0.04 second then a posterior infarction is present. In our experience, the width of the Q wave, and not the depth, is most important. A wide Q, 0.04 second or over, and especially when most of its width is produced by the downstroke, is always indicative of infarction regardless of its depth and regardless of whether the P was upright or inverted. However, the depth is also important in the diagnosis of infarction if the P wave is upright.

The importance of the width of the Q wave is shown in Fig. 10, which reveals the tracings of a patient with a typical history of myocardial infarction. On Dec. 28, 1948 a few hours after the attack, an electrocardiogram taken was essentially normal except for a slight S-T elevation in Lead aV_L. The following day (Dec. 29, 1948) Lead aV_L showed a Q wave which is 0.04 second in width and thick on its down stroke and there is S-T elevation with some coving of the T wave. Serial tracings taken up to Jan. 14, 1949 prove the diagnosis of myocardial infarction as is shown by the S-T and T wave changes in Lead aV_L. The usual chest leads (V_2 through V_6) were normal on all occasions. On Jan 8, 1949 high chest leads were taken in the V_4, V_5, high anterior, high midaxillary, and high posterior axillary lines which show inverted T waves. Thus we can localize the infarct as being high lateral in position. The patient returned three months later on April 27, 1949 for a follow up electrocardiogram. As is seen in Fig. 10 only the remnants of the healed infarct are seen, that is a wide, thick Q and an inverted T wave in Lead aV_L.

Normal Inverted T Waves: Normally, T waves may be inverted in Leads aV_F and aV_L when the R is less than 5 mm. in heighth. However, we have found that, in addition, even though the R is 5 mm. or over, the T may be flat or inverted if initially a cavity Q wave but not a septal Q wave is present. In these cases, all other leads are normal. We have also found that when the limb electrode faces the transitional or septal zone, the T may be flat or inverted.

<div align="center">SUMMARY</div>

I. Q Waves

The width and slurring of the Q wave especially in its downstroke and not the depth has been found by us to be most important in determining an infarction especially when preceded by an inverted P wave. However, if the P is upright, then the Q depth is also important.

An inverted P wave in aV_L does not exclude a myocardial infarct if followed by a slurred and widened Q wave of 0.04 second or more.

We were able to produce all types of cavity Q waves in aV_L by using only one subject and taking leads while he assumed various positions and during different respiratory phases.

We arrived at the following classification of normal Q waves.

1. In Lead aV_L:
A. Septal Q
B. Endocardial or cavity Q as seen in vertical hearts.
2. In Lead aV_F:
A. Septal Q.

B. QS type in a very horizontal heart and when the electrode is perpendicular to initial septal impulse.

C. Cavity Q: Rare case when the apex rotates forward in a vertical heart and Lead aV_F faces cavity potential at the atrioventricular groove.

3. In Lead aV_R.—

A. QS Pattern: Lead aV_R usually shows a QS pattern except when it picks up an initial R from the septum or free right ventricular wall.

4. Precordial Semidirect Leads.—

A. Septal Q in left ventricular leads.

B. QS pattern in right ventricular leads in a very horizontal heart and when the electrode is perpendicular to the septal impulse and so does not record an initial R.

C. Deep Q waves in children in left ventricular leads.

II. *T Wave Pattern*

1. In Leads aV_L and aV_F.—

A. Normally, T waves may be flat or inverted in these leads if the R is less than 5 mm. in heighth. However, in cases where the lead faces cavity potential and so reveals an initial Q, other than septal, then no matter how high the R, the T wave may be flat or inverted.

B. Transitional or septal T. If these leads face this area, then the T may be flat or inverted.

2. In Lead aV_R.—

A. Normally, the T is always inverted. If upright, then disease is always present. However, a negative T does not exclude disease.

3. Precordial Indirect Leads.—

The T is usually up, except in children when the right ventricular leads may have inverted T waves.

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THE Q WAVE IN ESOPHAGEAL ELECTROCARDIOGRAPHY

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E sophageal electrocardiography affords the closest anatomical approach to the study of potentials of the human left ventricle without resorting to more complex procedures such as intracardiac catheterization. In general, three recognizable zones with distinct electrocardiographic patterns exist in esophageal leads. The ventricular zone, recorded in lower esophageal leads which reflect the potentials of the diaphragmatic and posterior aspects of the left ventricle, usually shows an upright P wave and an RS or R pattern which may be preceded by a small Q wave.[1-3] At the atrial zone the P wave becomes diphasic and shows a sharp intrinsic deflection[4,5] while the ventricular complex is QS or Qr in configuration. The latter reflects left ventricular cavity potentials. In the supra-atrial zone inversion of all complexes is found.

It was with the aim of defining the significance of Q waves in Lead III and aV_F that the esophageal approach was utilized as an aid in the study of posterior myocardial infarction.[1,2,6-9] The presence of an atrial intrinsic deflection has been regarded as indicating that the electrode is over the left atrium. The ventricular pattern as recorded at this level represents left ventricular cavity potential. The absence of the atrial intrinsic deflection has been regarded as indicating that the electrode is over the surface of the ventricle. In the absence of an intrinsic atrial deflection, the presence of a Q wave 0.4 mv. or more in depth or 20 per cent or more of the voltage of the R wave has been suggested as a criterion for the diagnosis of posterior wall infarction.[8] Infarctions of the diaphragmatic aspect of the heart are usually adequately reflected in Lead aV_F.[2,8] In clinically suspected cases of posterior wall infarction which did not show the characteristic electrocardiographic changes in Lead aV_F, the presence of a Q wave, abnormal by the above criteria, has been considered diagnostic of infarction located high on the posterior myocardial wall, near the atrial margin.[2,8] However, it has recently been questioned whether Q waves considered abnormal by the above standards may not be seen in persons without infarction.[9]

The present study was undertaken to evaluate further the significance of the Q wave in esophageal leads.

METHODS

The subjects of this study included fifteen individuals with posterior wall infarction as diagnosed by an abnormal Q wave (25 per cent or more of the R wave[2]) in Lead V_F associated with a history and typical clinical course of previous myocardial infarction due to coronary occlusion, and sixty patients with normal hearts and patients with enlarged hearts without any evidence or history
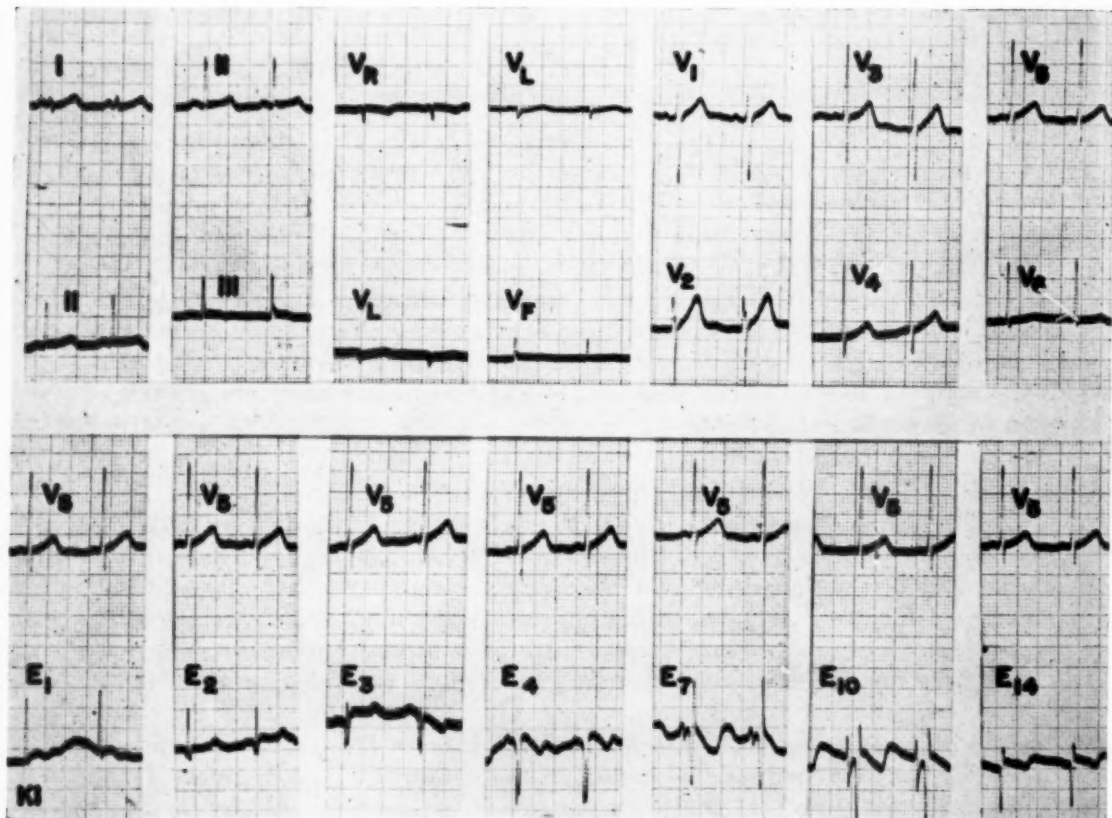
Fig. 1.—A 20-year-old man with no history of cardiac disease. The heart was normal on examination. E_1-E_4 are recorded at lower esophageal level. Note prominent Q wave in E_3 and QS in E_4, in the absence of an atrial intrinsic deflection. Atrial intrinsic deflection is present in E_7 and E_{10}. E_1 is similar to V_F. E_{14} is recorded at the supracardiac level.

of infarction. The esophageal electrode employed in this study consists of a rubber tube with a central core of fifteen fine wires, each of which is separately connected to external metal bands placed 1.75 cm. apart. By means of this rubber tube, the end of which was placed at least 6 cm. below the level of the diaphragm under fluoroscopic control, a regular sequence of fifteen esophageal electrocardiographic patterns was recorded in each patient. The segment of the heart thus studied usually included the area from the diaphragmatic surface up to and including the level of the great vessels. A Technicon 3 channel cardio-

graph was utilized to permit timing and evaluation of initial deflections in simultaneous leads.   With the aid of a Technicon external selector it was possible to record simultaneous standard, esophageal, unipolar extremity, and precordial leads.   An electrical filter as described elsewhere[10,11] was employed to eliminate extraneous low-frequency potentials of gastric, esophageal, and diaphragmatic origin, so that a satisfactory record could be obtained.   Lead V_F, as employed in this study, consisted of a Wilson unipolar extremity lead taken at 1.5 times the usual sensitivity.
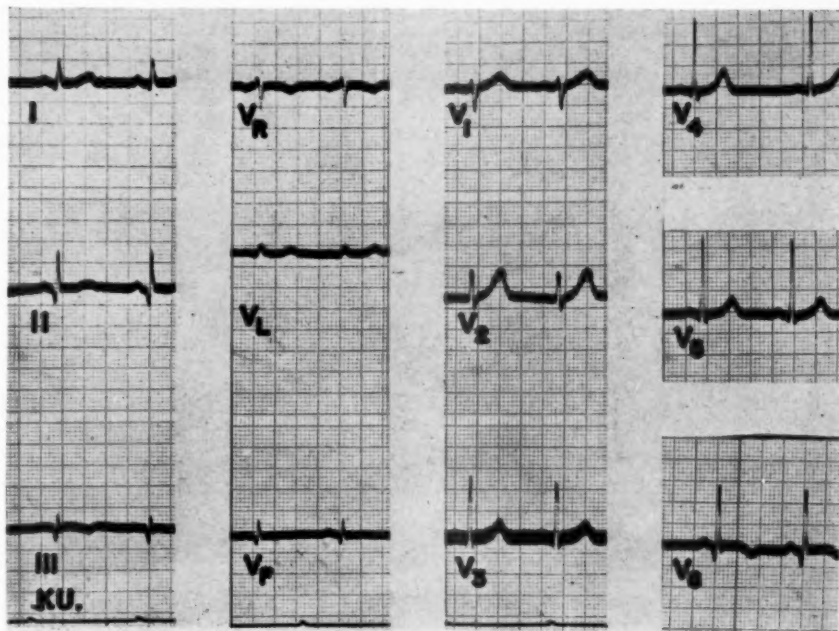
Fig. 2.—A 54-year-old man with myocardial infarction eight years previously, and with angina pectoris. Deep Q wave in Leads II, III, and V_F.

RESULTS

The lower esophageal leads which reflect the posterior and diaphragmatic surfaces of the heart usually reveal upright P waves.   The ventricular complex is represented by an R or RS pattern which not infrequently is preceded by a small Q wave.   At a slightly higher level, opposite the left atrium, intrinsic diphasic atrial waves and QS or QR patterns are present which represent left ventricular cavity potentials.   Above this level the P wave is inverted and a QS pattern is usually present.

In normal individuals without a history and electrocardiographic evidence of infarction, and in patients with cardiac hypertrophy without infarction, a Q wave 25 per cent or more of the voltage of the R wave or 0.4 mv. or more in depth was not infrequently found in lower esophageal leads in the absence of an intrinsic atrial deflection (Fig. 1).

In several cases of right ventricular hypertrophy without infarction, a QR or QS pattern was found in lower esophageal leads at the ventricular zone. In some of these patients a similar pattern was obtained with an intracardiac lead in the cavity of the right ventricle and in the inferior vena cava.

In all cases with posterior wall infarction, abnormal Q waves were present in esophageal leads at the ventricular zone (Figs. 2 and 3).
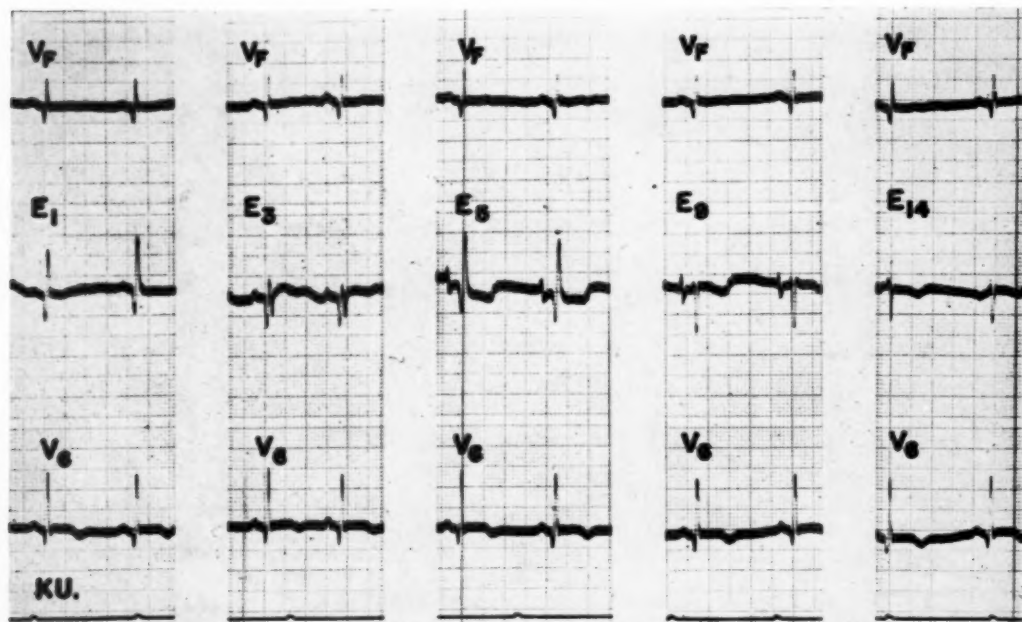
Fig. 3.—Same patient as Fig. 2. E_1-E_3 are recorded at lower esophageal level.   Deep Q wave is in E_1 and E_3, in the absence of an atrial intrinsic deflection.   Note similarity of E_1 and V_F.   Atrial intrinsic deflection is present in E_5 and E_9. E_{14} is recorded at supracardiac level.   Note similarity of E_3 in this patient and in the normal patient in Fig. 1.

The esophageal electrocardiographic pattern reflecting the diaphragmatic surface of the heart in normal individuals and in patients with and without infarction was consistently reflected in Lead V_F.

COMMENTS

The acceptance by some investigators[1-3,12] of certain distances in centimeters from the nares as representing atrial (35 to 40 cm.) or ventricular (45 to 55 cm.) levels, is not without its pitfalls.   The distances of the various cardiac chambers from the nares vary considerably in individuals because of differences in body build, cardiac size, and cardiac position.   Since the electrocardiographic pattern undergoes considerable change within short esophageal segments (2 to 4 cm.), it seems inadvisable to employ prescribed distances from the nares as criteria for atrial and ventricular potentials.   The introduction of the esophageal electrode under fluoroscopic control and the recording of a regular sequence of fifteen esophageal electrocardiograms, as employed in this investigation, facilitate the accurate appraisal and study of the various complexes.

The left leg electrode, being at some distance from the heart, reflects the potentials of a preponderant part of the diaphragmatic cardiac surface.[13] The introduction of the central terminal of Wilson[14] into electrocardiography has made possible the recording of potentials of a smaller area of the heart essentially uninfluenced by potentials of more distant parts of the heart. This fact led to the usage of unipolar leads in esophagel electrocardiography in mapping the electrocardiographic topography of the diaphragmatic and posterior surfaces of the left ventricle.[1,2,12,15] In the present investigation, Lead V_F was essentially similar to the patterns recorded by the lower esophageal electrodes, reflecting the diaphragmatic surface of the heart. A deep Q wave in Lead V_F is also recorded in the lower esophageal leads, while in those cases where the Q wave was of questionable significance in V_F, a similar questionable Q wave was obtained in the lower esophageal leads. From the data of this investigation, and those of others,[2,8,13,16] it is evident that the potentials of the diaphragmatic aspects of the heart are consistently and adequately reflected in the left leg electrode (V_F). Hence, evidence of infarction involving the diaphragmatic aspects of the heart appears in Lead V_F. It was hoped that multiple esophageal leads would aid in the diagnosis of localized posterior wall infarction, especially at the auricular margin,[2] much in the same way that multiple precordial leads have been utilized in the diagnosis of localized anterior wall infarcts.[1] Though the finding of a deep Q wave, 25 per cent or more of the R wave, in esophageal leads without the presence of an intrinsic atrial deflection and without an abnormal Q wave in Lead V_F, may indicate localized posterior infarction, such patterns may also be seen in normal individuals.

The diagnosis of infarction usually rests upon the finding of a deep Q wave in leads over the infarcted portions of the ventricular wall. These Q waves represent potential changes essentially identical with those that occur in the ventricular cavity and are due to the absence of electromotive forces normally produced by the outward propagation of the wave of excitation in noninfarcted cardiac muscle under the electrode.[17] Essentially similar complexes representing left ventricular cavity potentials are obtained when the esophageal lead is over the left atrium.[1,5] The ventricular complex at the atrial level usually consists of a QR or QS pattern, the latter being similar to the pattern recorded within the left ventricular cavity in animals and by catheterization of the left ventricle in humans.[18]

In the infra-atrial zone, the region between the atrial margin and the diaphragm, the finding of a QS or QR pattern without an intrinsic atrial deflection was not infrequent in patients without infarction. Although these Q waves may represent cavity potentials transmitted through an infarct of the posterior portion of the left ventricle acting as an electrical "window," these Q waves are indistinguishable in either timing or duration from those seen in this zone in patients without infarction. In the latter group the QR complexes represent a mixture of left ventricular cavity and surface potentials.

The presence of deep Q waves in right ventricular hypertrophy probably indicates right ventricular potentials transmitted through the inferior vena cava,

since similar patterns were obtained by an intracardiac electrode in the right ventricular cavity and the inferior vena cava.[19]

These observations confirm and extend those of others[9] in demonstrating the difficulty of interpreting a QR or QS pattern in esophageal leads, especially in the absence of characteristic changes in V_F. Further studies are being pursued to determine the complete esophageal electrocardiographic patterns in normal and in abnormal conditions.

CONCLUSIONS

1. Deep Q waves may be found in the absence of an intrinsic atrial deflection in lower esophageal leads in patients without infarction.

2. Lead V_F consistently reflects the electrocardiographic pattern of the diaphragmatic surface of the heart.

3. The difficulties encountered in the interpretation of esophageal electrocardiograms in the diagnosis of localized posterior wall infarctions have been discussed.

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THE COMPARATIVE VALUE OF THE AUGMENTED UNIPOLAR LIMB LEADS VERSUS THE STANDARD LIMB LEADS IN MYOCARDIAL INFARCTION

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THE introduction of the central terminal electrode by Wilson is truly one of the great forward steps in electrocardiography. The modification, in recent years, by Goldberger[1,2] and the subsequent popularization of "unipolar electrocardiography" (since the major objection of low voltage was overcome) have served to carry abroad the theory of electrocardiac effects propounded by Wilson and his group.

Because of the obvious advantages of unipolar electrocardiography, in recent years there seems to have been a tendency to minimize the value of our old stand-by, the standard limb leads. Though studies have been made along the lines of the present report,[3,4] nevertheless, it appeared to the author that the problem was sufficiently unsettled to warrant further investigation. Consequently, the present study was undertaken to determine the relative merit of the standard limb leads against the unipolar limb leads (augmented), in the diagnosis of myocardial infarction.

METHOD

Twenty-five consecutive cases were selected which showed autopsy evidence of myocardial infarction, and in which twelve leads were available, the twelve leads being: I, II, III, aV_R, aV_L, aV_F, V_1, V_2, V_3, V_4, V_5, and V_6. Of these twenty-five cases, five had to be discarded (for the purposes of this study), because of the presence of bundle branch block. Of the remaining twenty cases, there were eight cases of anterior myocardial infarction, seven cases of posterior myocardial infarction, and five cases of both anterior and posterior myocardial infarction. Of the cases of anterior infarction, there were eight (of thirteen) with anteroseptal infarction (Cases 1, 2, 3, 4, 6, 8, 17, and 18) and five with antero-lateral infarction (Cases 5, 7, 16, 19, and 20). Each case was studied as illustrated in Table I, and correlated with the autopsy findings.

TABLE I. CASE 20, R. W. DEA.

LEAD	P HEIGHT (MM.)	P WIDTH (MM.)	PR (SEC.)	QRS (SEC.)	Q HEIGHT (MM.)	Q WIDTH (MM.)	R HEIGHT (MM.)	R WIDTH (MM.)	S HEIGHT (MM.)	S WIDTH (MM.)	ST (MM.)	T (MM.)	REMARKS
I	1.0	0.08	0.16	0.08	-0.25	0.03	1.5	0.05	0.0	0.0	0.0	-3.0	
II	2.0	0.12	0.20	0.08	-2.0	0.04	1.0	0.04	0.0	0.0	0.25	-1.0	
III	1.25	0.10	0.20	0.08	-2.0	0.03	0.0	0.02	-2.0	0.03	0.0	+2.5	Notched QS
aV_R	-1.0	0.09	0.19	0.07	0.0	0.0	1.0	0.03	-1.5	0.04	–	-2.5	
aV_L	±	0.08	0.20	0.06	0.0	0.0	2.0	0.06	-0.5	0.04	0.0	+1.0	
aV_F			0.19	0.09	-2.0	0.03	0.0	0.02	0.0	0.0	+	+2.5	Notched QS
V_1	1.5	0.10	0.20	0.07	-7.0	0.07	0.0	0.0	0.0	0.0	+1.0	+4.0	QS
V_2	0.5	0.08	0.20	0.08	-23.0	0.08	0.0	0.0	0.0	0.0	+2.0	+3.0	QS
V_3	0.5	0.08		0.08	-20.0	0.08					+2.0	-1.0	QS
V_4	1.0	0.10	0.19	0.12	-7.0	0.12	0.0	0.0	0.0	0.0	+0.5	-5.0	Notched QS
V_5	0.75	0.09	0.20	0.12	-1.0	0.03	3.0	0.05	-1.0	0.04	0.0	-6.0	
V_6	1.0	0.06	0.20	0.10	-0.5	0.02	4.0	0.05	-0.5	0.03	0.0	-3.0	

Auricular rate: 75
Ventricular rate: 75
Rhythm: sinus
Axis deviation: indeterminate
PR interval: 0.20 sec.
QRS interval: 0.08 sec.
P waves: upright
QRS complexes: Q_2, Q_3, small Q_1; low voltage
T waves: T_1 and T_2 inverted
ST segments: ST_2 slightly elevated
aV_R: early R wave; T upright
aV_L: T inverted; Q absent
aV_F: deep Q wave
V_1: QS
V_2: QS
V_3: QS; diphasic T
V_4: notched QS; T inverted
V_5: deep Q wave; T inverted
V_6: Q with inverted T wave
Interpretation: old posterior myocardial infarction with recent anterolateral myocardial infarction

Remarks: Patient died Dec. 4, 1948
Electrocardiogram taken Nov. 30, 1948
Age: 49 years
Height: 70 inches
Weight: 185 pounds
Blood pressure: 120/70
Lead I: small Q_1; T_1 inverted
Lead aV_L: Q absent; T inverted
Lead III: Q wave present
Lead aV_F: Q wave present
Lead I better than aV_L, but diagnosis of anterolateral infarct can be made by chest leads
Lead III and Lead aV_F of equal value
Autopsy Dec. 7, 1948:   varying aged infarction, involving posterior wall of left ventricle and recent anterolateral infarct.

TABLE II.   Showing the Greater Diagnostic Value, in General, of aV$_L$ Over Lead I in Anteroseptal Infarction, and the Greater Diagnostic Value of Lead I Over aV$_L$ in Anterolateral Infarction (In Either Case, the Chest Leads are Diagnostic—See Fig. 1)

CASE NO.	LEAD	DEPTH OF Q (MM.)	WIDTH OF Q (MM.)	HEIGHT OF R (MM.)	%Q IS OF R	ALGEBRAIC VOLTAGE QRS	TALLEST R LEAD	TALLEST R HEIGHT (MM.)	% Q IS OF TALLEST R	REMARKS
1	aV$_L$	1.0	0.02	3.5	28.6	+2.5	aV$_L$	3.5	28.6	Anteroseptal
	I	0.125	0.02	3.0	4.2	+2.875	I	3.0	4.2	
2	aV$_L$	1.0	0.04	9.0	11.1	+8.0	aV$_L$	9.0	11.1	Anteroseptal
	I	0.25	0.02	3.0	8.3	+2.25	I	3.0	8.3	
3	aV$_L$	5.0	0.08	0.0	∞	-5.0	aV$_L$	8.0	∞	Anteroseptal
	I	—	0.02	+	100.0	-1.5	III	8.0	0+	
4	aV$_L$	1.0	0.04	6.0	16.7	+5.0	aV$_L$	6.0	16.7	Anteroseptal
	I	1.0	0.03	4.0	25.0	+3.0	I	4.0	25.0	
5	aV$_L$	0.5	0.03	6.0	8.3	+5.5	aV$_L$	6.0	8.3	Anterolateral
	I	2.0	0.04	3.5	57.0	+1.5	I	3.5	57.0	
6	aV$_L$	0.75	0.04	9.0	8.3	+8.25	aV$_L$	9.0	8.4	Anteroseptal
	I	0.0	0.0	7.0	0	+7.0	I	7.0	0	
7	aV$_L$	1.5	0.04	0.0	∞	-1.5	II	9.5	15.8	Anterolateral
	I	1.0	0.03	4.5	22.2	+3.5	II	11.5	8.7	
8	aV$_L$	0.5	0.04	5.0	10.0	+4.5	aV$_L$	5.0	10.0	Anteroseptal
	I	—	0.02	3.5	0+	+3.5	II	7.0	0+	
16	aV$_L$	2.0	0.04	0.0	∞	-2.0	aV$_F$	10.0	20.0	Anterolateral
	I	1.5	0.04	3.0	50.0	+1.5	II	11.0	13.6	
17	aV$_L$	0.0	0.0	2.0	0	+2.0	aV$_L$	2.0	0	Anteroseptal
	I	0.0	0.0	2.0	0	+1.5	I	2.0	0	
18	aV$_L$	0.0	0.0	4.0	0	+4.0	aV$_L$	4.0	0	Anteroseptal
	I	0.0	0.0	5.0	0	+5.0	I	5.0	0	
19	aV$_L$	0.0	0.0	1.0	0	-4.0	aV$_F$	5.5	0	Anterolateral
	I	0.25	0.02	1.0	25.0	-1.75	III	7.5	3.0	
20	aV$_L$	0.0	0.0	2.0	0	+2.0	aV$_L$	2.0	0	Anterolateral
	I	0.25	0.03	1.5	16.7	+1.25	I	1.5	16.7	

Table III. Showing the Greater Diagnostic Value, in General, of Lead III Over aVF in Posterior Infarction (See Fig. 1)

CASE NO.	LEAD	DEPTH OF Q (MM.)	WIDTH OF Q (MM.)	HEIGHT OF R (MM.)	%Q is OF R	ALGEBRAIC VOLTAGE QRS	TALLEST R		%Q IS OF TALLEST R	REMARKS
							LEAD	HEIGHT (MM.)		
9	aVF	6.0	0.05	12.0	50.0	+6.0	aVF	12.0	50.0	Posterior
	III	10.0	0.04	11.0	91.0	+1.0	II	13.5	74.1	
10	aVF	0.25	0.02	5.0	5.0	+4.75	aVF	5.0	5.0	Posterior
	III	1.5	0.04	5.0	30.0	+3.5	III	5.0	30.0	
11	aVF	4.0	0.04	4.0	100.0	0.0	aVL	9.0	44.4	Posterior
	III	13.0	0.04	3.0	433.3	-10.0	I	14.0	93.0	
12	aVF	Low voltage—not readable	0.04	+	∞	-2.0	I	6.0	33.3	Posterior
	III									
13	aVF	2.0	0.04	5.0	60.0	+1.5	aVF	5.0	60.0	Posterior
	III	3.0	0.04	7.0	71.4	+2.0	II	9.0	55.5	
14	aVF	5.0	0.06	5.0	60.0	+2.0	aVL	6.0	50.0	Posterior
	III	3.0	0.07	4.5	156.0	-2.5	I	6.0	116.7	
15	aVF	7.0	0.06	9.0	27.8	+6.5	aVF	9.0	27.8	Posterior
	III	2.5	0.04	8.0	87.5	+1.0	I	8.5	82.5	
16	aVF	7.0	0.03	10.0	15.0	+8.5	aVF	10.0	15.0	Posterior
	III	1.5	0.03	9.0	55.5	+8.5	II	11.0	4.6	
17	aVF	0.5	0.02	0.0	∞	-5.0	aVL	2.0	100.0	Posterior
	III	2.0	0.02	-0.5	—	-7.0	I	2.0	125.0	
18	aVF	2.5	0.03	1.0	150.0	-5.0	aVL	4.0	37.5	Posterior
	III	1.5	0.08	0.0		-6.0	I	5.0	120.0	
19	aVF	6.0	0.04	5.5	18.2	+4.5	aVF	5.5	18.2	Posterior
	III	1.0	0.04	7.5	13.4	+6.5	III	7.5	13.1	
20	aVF	1.0	0.03	0.0	∞	-2.5	aVL	2.0	100.0	Posterior
	III	2.0	0.03	0.0	∞	-4.0	I	1.5	75.0	

Table IV. Summarizing Findings in Tables II and III

	NO. AND %	REMARKS
$Q aV_L > Q_1$	7/13=53.9%	
$Q aV_L = Q_1$	3/13=23.1%	
Width of $Q aV_L$ > width of Q_1	6/13=46.2%	Q absent in two cases
Width of $Q aV_L$ = width of Q_1	4/13=30.7%	Q absent in two cases
$R aV_L > R_1$	7/13=53.9%	
$R aV_L = R_1$	7/13=53.9%	
$\%Q aV_L$ of $R aV_L > \%Q_1$ of R_1	2/13=15.4%	
$\%Q aV_L$ of $R aV_L = \%Q_1$ of R_1	7/13=53.9%	Q absent in both cases
Algebraic voltage of aV_L > algebraic voltage of I	2/13=15.4%	
Algebraic voltage of aV_L = algebraic voltage of I	7/13=53.9%	
	0/13= 0.0%	Three were negative quantities
Tallest R aV' leads > tallest R I, II, III	6/13=46.2%	
$\%Q aV_L$ of tallest R aV > $\%Q_1$ of tallest R I, II, III	7/13=53.9%	
Tallest R aV leads = tallest R I, II, III	2/13=15.4%	
$\%Q aV_L$ of tallest R aV = $\%Q_1$ of tallest R I, II, III	2/13=15.4%	Q absent in both cases
$Q_3 > Q aV_F$	9/12=75.0%	
$Q_3 = Q aV_F$	2/12=16.7%	
Width of Q_3 > width of $Q aV_F$	4/12=33.3%	
Width of Q_3 = width of $Q aV_F$	6/12=50.0%	
$R aV_F > R_3$	8/12=66.7%	R absent in one case
$R aV_F = R_3$	2/12=16.7%	QS
$\%Q_3$ of $R_3 > \%Q aV_F$ of $R aV_F$	9/12=75.0%	
$\%Q_3$ of $R_3 = \%Q aV_F$ of $R aV_F$	1/12= 8.3%	
Algebraic voltage of aV_F > algebraic voltage of III	9/12=75.0%	
Algebraic voltage of aV_F = algebraic voltage of III	1/12= 8.3%	
Tallest R I, II, III > tallest R aV leads	7/12=58.3%	
$\%Q_3$ of tallest R I, II, III > $\%Q aV_F$ of tallest R aV	8/12=66.7%	
Tallest R I, II, III = tallest R aV leads	3/12=25.0%	
$\%Q_3$ of tallest R I, II, III = $\%Q aV_F$ of tallest R aV	0/12= 0.0%	

Results.—The significant findings are tabulated (Tables II, III, and IV).
Anterior Infarction.—

1. In anterior infarction, there were only three cases (23.1 per cent) in which Q_1 was greater than Q aV_L (Cases 5, 19, and 20), and these were all in cases of anterolateral infarction.

2. In two of the above three cases, Q aV_L was absent (Cases 19 and 20).

3. In two cases of anterior infarction (15.4 per cent) Q was absent in both aV_L and I, the diagnosis being made with the chest leads (Cases 17 and 18).

4. In no case of anteroseptal infarction was Q_1 deeper than Q aV_L.

5. Of four cases of anterolateral infarction, T_1 and T aV_L were equally inverted in one (Case 5) and T_1 was more deeply inverted in two (Cases 16 and 20).

6. Of the cases of anteroseptal infarction, T_1 was deeper than T aV_L in only two (Cases 1 and 8), and the T waves were equal in two (Cases 3 and 6).

7. In seven cases of anterior infarction, Q aV_L was greater than Q_1 (Cases 1, 2, 3, 6, 7, 8, and 16). Only one of these (Case 16) was a case of anterolateral infarction.

8. In seven cases of anterior infarction, R aV_L was greater than R_1 (Cases 1, 2, 4, 5, 6, 8, and 20); in three cases R aV_L was absent (Cases 3, 7, and 16); in two cases R aV_L equalled R_1 (Cases 17 and 19); one (Case 18) had absent Q aV_L and Q_1, and R_1 was greater than R aV_L.

9. In seven cases, the per cent Q aV_L of R aV_L was greater than the per cent Q_1 of R_1 (Cases 1, 2, 3, 6, 7, 8, and 16).

10. Of four cases where per cent Q_1 of R_1 was greater than per cent Q aV_L of R aV_L (Cases 4, 5, 19, and 20), Q aV_L was absent in two cases (Cases 19 and 20), and of the other two cases one was anteroseptal (Case 4) and one was anterolateral (Case 5).

11. In seven cases of anterior infarction, the algebraic sum of the voltage in aV_L was greater than that in Lead I (Cases 2, 4, 5, 6, 8, 17, and 20). In the other six cases the reverse was true, but four of these were negative quantities (Cases 3, 7, 16, and 19).

12. In six cases (46.2 per cent) the tallest R wave of the augmented unipolar limb leads was taller than the tallest R wave of the standard limb leads (Cases 1, 2, 4, 5, 6, and 20).

13. In seven cases (53.9 per cent) the per cent Q of the tallest R was greater in the augmented unipolar limb leads than in the standard limb leads (Cases 1, 2, 3, 6, 7, 8, and 16).

In general: (a) In anteroseptal infarction, (1) Q aV_L is deeper than Q_1; (2) per cent Q aV_L of R aV_L is greater than per cent Q_1 of R_1; (3) per cent Q aV_L of the tallest R aV is greater than per cent Q_1 of the tallest R in the standard limb leads; (b) In anterolateral infarction, (1) Q_1 is deeper than Q aV_L; (2) per cent Q_1 of R_1 is greater than per cent Q aV_L of R aV_L; (3) T_1 tends to be deeper than T aV_L.

Posterior Infarction.—There were twelve cases of posterior infarction (Cases 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, and 20).

1. In nine cases (75 per cent), Q_3 was deeper than Q aV_F (Cases 9, 10, 11, 12, 13, 14, 15, 17, and 18). In four of these cases, Q_3 was also wider than Q aV_F (Cases 10, 12, 14, and 18).

2.   In two more cases, Q_3 equalled Q aV_F in depth (Cases 19 and 20), and in only one case was Q aV_F deeper than Q_3 (Case 16).

3.   In seven cases (58.3 per cent) R aV_F was taller than R_3 (Cases 9, 11, 14, 15, 16, 17, and 18) and in two cases they were equal (Cases 10 and 20).

4.   Consequently, in nine cases (75 per cent) per cent Q_3 of R_3 was greater than per cent Q aV_F of R aV_F (Cases 9, 10, 11, 12, 13, 14, 15, 16, and 18), with one equal (20).

5.   In nine cases (75 per cent) the total voltage of aV_F was greater than in Lead III (Cases 9, 10, 11, 12, 14, 15, 17, 18, and 20).

6.   The tallest R wave of the standard limb leads was greater than the tallest R wave of the augmented unipolar limb leads in seven cases (58.3 per cent), (Cases 9, 11, 12, 13, 16, 18, and 19), and equal in three cases (25 per cent) (Cases 10, 14, and 17).

7.   The per cent Q_3 of the tallest R wave of the standard limb leads was greater than the per cent Q aV_F of the tallest R aV in eight cases (66.7 per cent) (Cases 9, 10, 11, 12, 14, 15, 17, and 18).

8.   In one (Case 12), aV_F was of such low voltage as to be unreadable.

In general: (*a*) In posterior infarction, (1) Q_3 is deeper than Q aV_F; (2) per cent Q_3 of R_3 is greater than per cent Q aV_F of R aV_F; (3) per cent Q_3 of the tallest R wave of the standard limb leads is greater than per cent Q aV_F of the tallest R aV.

<div align="center">DISCUSSION</div>

It has been stated that Q aV_F is more significant than Q_3 because it is the source of Q_3.[1,3]   In other words, Q_3 cannot be greater than Q aV_F, except as it is influenced by R aV_L, and so Q_3 is less specific than Q aV_F.

By the same token, Q aV_L is said to be more significant than Q_1, because it is the source of Q_1.   Thus Q_1 cannot be greater than Q aV_L, except as it is influenced by R aV_R, and so Q_1 is less specific than Q aV_L.

It is evident, since in general, Q aV_L is greater than Q_1 and since Q_3 is greater than Q aV_F, that the specificity of a Q wave as determined by the above reasoning is not the only factor to be considered in the diagnosis of myocardial infarction.   We must also consider the usefulness of the various Q waves in diagnosis, even if these Q waves *are* influenced by R waves (R aV_R in the case of Q_1 and R aV_L in the case of Q_3). Q_1 is generally smaller than Q aV_L because there is generally no early R aV_R, but rather a Q aV_R.   It is because Q_1 is smaller than Q aV_L (except in anterolateral infarction) that it is *not as valuable as* Q aV_L in such cases.   By the same reasoning, since Q aV_F is generally smaller than Q_3, Q aV_F is *not as valuable as* Q_3 in the diagnosis of posterior infarction.

It could be argued that since Q aV_F is smaller than Q_3, it is more specific, giving rise to fewer "false positives."   However, this would force us to conclude, since Q_1 is generally smaller than Q aV_L, that Q_1 is more specific than Q aV_L and would give rise to fewer "false positives."   As a matter of fact, we know clinically that Q aV_L is more valuable than Q_1 in diagnosing anterior infarction (because of its greater dimensions, not because of any greater specificity), and, similarly, Q_3 is more valuable than Q aV_F in diagnosing posterior infarction because of its greater size rather than becaue of any greater specificity.   (See Fig. 1.)

Without debating the perfectly obvious fact that the augmented unipolar limb leads are superior to the standard limb leads in theory and in the understanding of electrocardiographic mechanisms, it appears that: (1) Lead III is more useful than Lead aV_F in cases of posterior infarction; (2) though Lead aV_L is more informative than Lead I in anteroseptal infarction (and inferior to it in anterolateral infarction), the chest leads in these cases are superior to both.
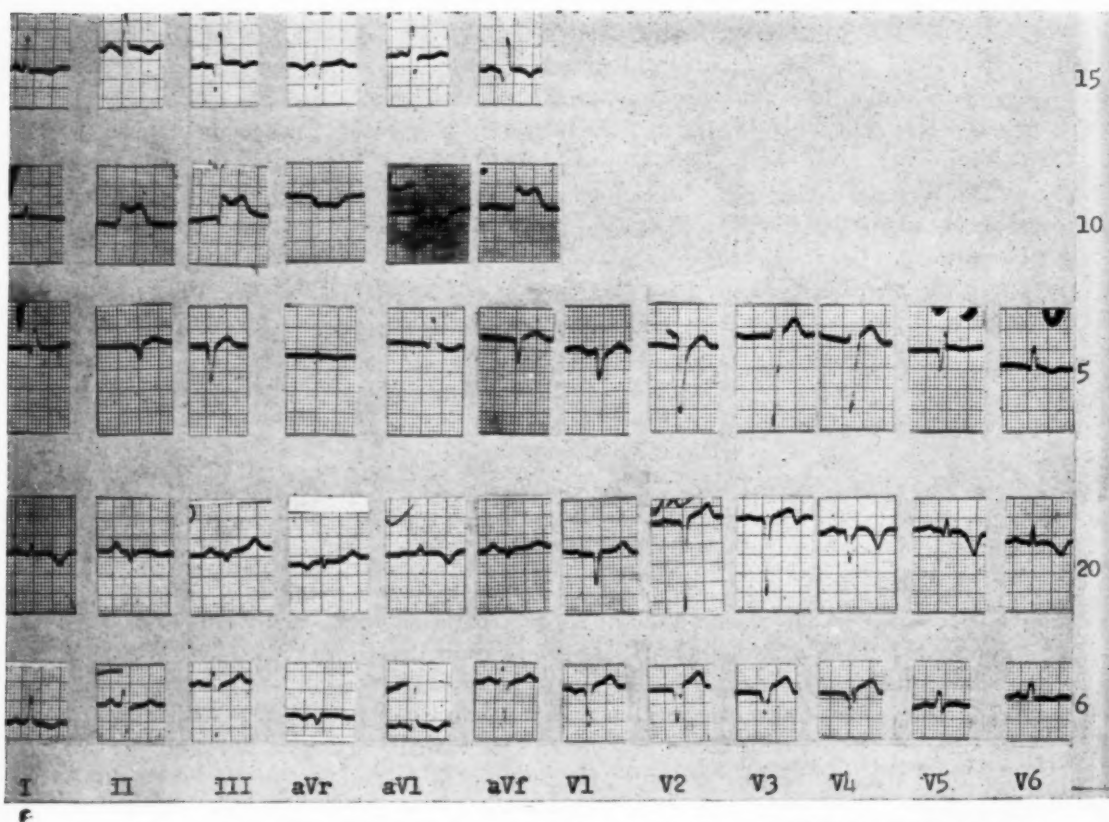

Fig. 1.—Cases 15 and 10 illustrate the greater value of Lead III over Lead aV_F in posterior infarction. Case 5 illustrates the greater value of Lead I over Lead aV_L in anterolateral infarction. Case 6 illustrates the greater value of Lead aV_L over Lead I in anteroseptal infarction. In both Cases 5 and 6, the diagnosis is made in the precordial leads. Case 20 shows both posterior and anterolateral infarction in the same tracing (see Table I).

As previously mentioned, specificity of Q waves, as determined above is not the only factor to be considered in the diagnosis of myocardial infarction. It is a very well-known fact that $Q\,aV_L$ may exist without anterior infarction and $Q\,aV_F$ may exist without posterior infarction. As a result, it has been found necessary to evaluate Q waves with respect to various empirical observations. This last statement applies to both the standard and the augmented unipolar limb leads.*

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*Paper in preparation.

The electrical position of the heart, as determined by the unipolar limb leads, is of theoretical value and of interest. However, this does not even imply clinical usefulness in the diagnosis of myocardial infarction. With all the discussion of unipolar limb leads as regards heart position and particularly specificity of Q waves, a point that seems to have been neglected is that the R waves of the unipolar limb leads which contribute to the formation of the Q waves of the standard limb leads may be more than mere passive agents. In other words, the *time of onset* of these R waves (in aV_R and aV_L) affects very significantly the contours of the standard limb leads. We know that the visible QRS complexes of the various leads do not all begin simultaneously in the electrocardiogram. Does not the existence of a posterior myocardial infarction influence the time of onset of R aV_L, and, by altering the instantaneous electrical axis, produce, perhaps, a taller R aV_L than existed prior to the infarction? This would result in a deeper Q_3 than expected, the resultant Q_3 being not less specific but actually more specific than Q aV_F.

By the same reasoning, an anterior myocardial infarction could alter the path of depolarization, change the instantaneous electrical axis, change the time of onset and the contour of QRS aV_R and, consequently, alter Q_1. These are not passive alterations, as frequently implied, but may actually be determining factors in the *value* of the various Q waves of the standard limb leads in the *clinical diagnosis* of myocardial infarction. Thus we see, that though Q_3 is greater than Q aV_F, this does not mean lack of specificity nor more frequent "false positives," but may actually mean greater specificity, over and above greater *clinical value*. In other words, two unipolar limb leads are *not necessarily* better than the standard limb lead which is their resultant.

It is, perhaps, surprising that lead aV_L is superior to Lead I in anteroseptal infarction and inferior to Lead I in anterolateral infarction. Since Lead aV_L is the left arm lead, it might be expected to be a lateral lead rather than a septal lead. However, if we consider the actual position of the heart and the fact that the septum actually lies in an almost frontal plane, it becomes evident that the septal effects are more readily projected to the left shoulder than are the lateral effects. With regard to this latter finding, it is of interest that since the conclusion of this study it has been possible, in numerous cases of anterior infarction, to determine whether the lesion was anterolateral or anteroseptal by comparing Leads I and aV_L, confirmation then being had in the V leads.

The series presented is too small from which to draw decisive conclusions, but it would appear that the problem is as yet still unsettled. It is hoped that other investigators with available facilities will continue to investigate this problem in order to see it closer to a solution.

CONCLUSIONS

1. Twenty-five cases are reported in which it was possible to compare the augmented unipolar limb leads with the standard limb leads, in cases with autopsy findings of myocardial infarction.

2.   For the purpose of diagnosing any but the most unusual types of myocardial infarction, where esophageal leads or multiple precordial leads in other than the usual six positions might be of help, the augmented unipolar limb leads, though helpful, do not appear necessary.

3.   As a routine procedure in the diagnosis of myocardial infarction, the standard limb leads and the precordial (unipolar) leads appear adequate and sufficient.

4.   The idea is introduced that R aV_R and R aV_L may be more than mere passive contributors to the formation of Q_1 and Q_3 and that these R waves may actually augment the specificity of the respective Q waves to which they contribute, rather than detracting from that specificity.

ADDENDUM

Since the completion of this paper, an article has appeared by E. Phillips and H. D. Levine in the February issue of the AMERICAN HEART JOURNAL (*A Critical Evaluation of Extremity and Precordial Electrocardiography in Acute Cor Pulmonale*, **39**:205, 1950). The findings of the authors included the conclusion that the unipolar limb leads were not likely to be as helpful as the standard limb leads in the diagnosis of cor pulmonale.

Another recent article along the lines of this report that should be mentioned is: Myers, and associates: *V. Correlation of Electrocardiographic and Pathologic Findings in Posterior Infarction* (AM. HEART J. **38**: 547, 1949).

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ACUTE CORONARY INSUFFICIENCY: PATHOLOGICAL AND PHYSIOLOGICAL ASPECTS

AN ANALYSIS OF TWENTY-FIVE CASES OF SUBENDOCARDIAL NECROSIS

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T HE recognition of a peculiar distribution and form of myocardial necrosis
limited in great part to the subendocardial musculature and papillary
muscles of the left ventricle, in the absence of a recent coronary artery occlusion,
has stimulated the survey of the anatomic alterations and the mechanisms responsible for their production.

The term subendocardial necrosis refers to the ischemic myocardial changes
predominantly of the left ventricle incident to deficiency in the coronary circulation. In the sense employed, these represent the myocardial alterations
resulting from a discrepancy between the requirements of the myocardium and
its available blood supply. This concept has been termed acute coronary insufficiency.[1-4] It is specifically restricted to indicate generally transient and
reversible insufficiency of coronary blood flow although the deleterious effects
upon the myocardium may be permanent. In striking contrast is acute coronary
artery occlusion which is preceded invariably by arteriosclerosis and is almost
always accompanied by extensive and usually well-localized myocardial infarction.[5]

MATERIAL AND METHODS

The material included in this study consists of twenty-five hearts which
disclosed evidence of recent myocardial change in the absence of acute coronary
artery occlusion. The specimens were studied in detail, both grossly and histologically. Sections of all portions of both left and right sides of the heart were
examined microscopically. These included anterior and posterior portions of
both ventricles, the interventricular septum, anterior and posterior papillary
muscles, and additional areas as indicated. The hearts were also carefully observed for disease of the valves, pericardium, and endocardium. Abnormalities
of the ascending aorta, sinuses of Valsalva, and the relationship of such changes
to the coronary ostia were also noted. The coronary arteries and their branches
were sectioned transversely at intervals of 1 to 3 mm. after fixation in formalin

or Kaiserling solution.   Arteriosclerotic segments were examined histologically, particularly zones which were severely narrowed or in which suspicion of recent change was raised grossly.   The following branches were examined closely:

A. Left coronary artery: anterior descending artery and its primary and secondary branches, the left circumflex artery and its branches to the anterior left ventricle, obtuse margin, posterior left ventricle, and, when present, the posterior descending branch.

B. Right coronary artery: right circumflex artery, and its branches to the anterior right ventricle, acute margin, posterior right ventricle, and when present, the posterior descending branch and the cross-over branch to the posterior left ventricle.

Fig. 1.—Photograph showing gross appearance of disseminated, confluent, hemorrhagic, and mottled subendocardial areas of necrosis; heart weight, 400 grams; coronary arteriosclerosis severe; spontaneous attack.

All hearts herein reported were examined by us personally.   The clinical records and the extracardiac pathological changes were studied for the evaluation of the various possible factors which might be concerned in the production of myocardial disease and coronary insufficiency.

MYOCARDIAL CHANGES

The pathological lesions of the myocardium, when grossly visible, generally consisted of isolated, disseminated, hemorrhagic or mottled yellowish-gray or

ANTERIOR

RIGHT **LEFT**

J.C. 13906

POSTERIOR
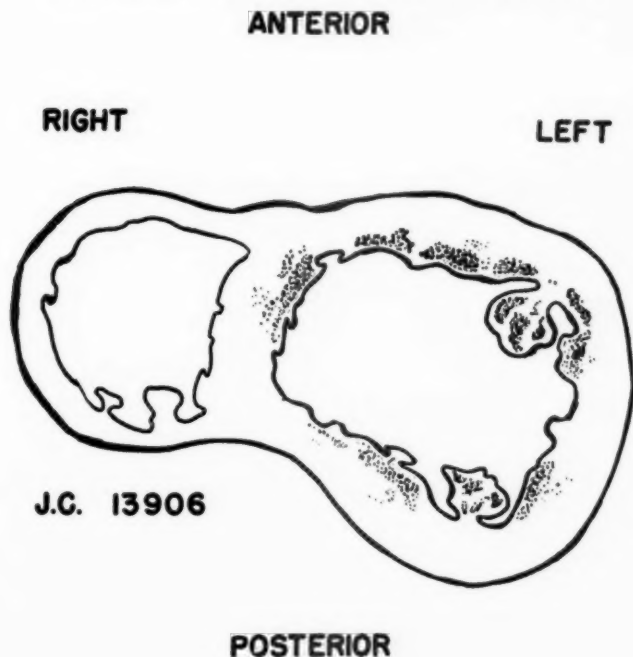
Fig. 2.—Diagram indicating distribution of widespread subendocardial necrosis. Same case as Fig. 1

ANTERIOR
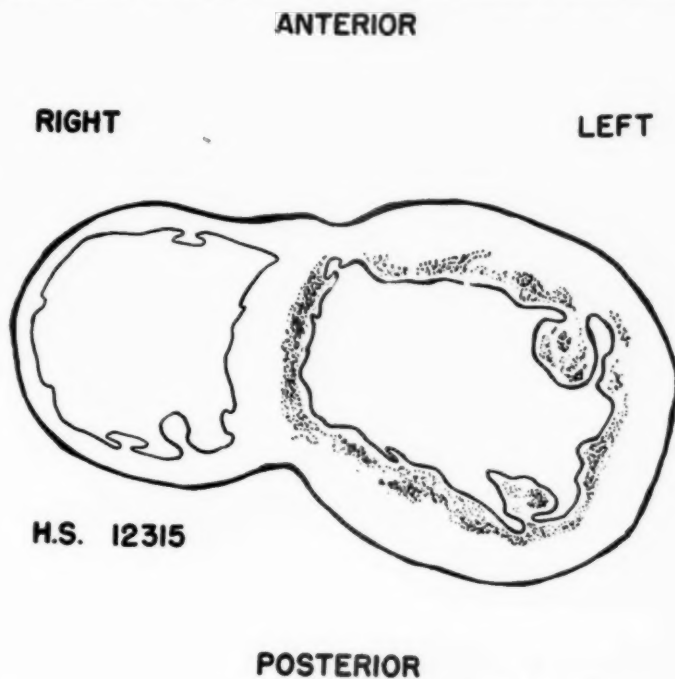
RIGHT **LEFT**

H.S. 12315

POSTERIOR

Fig. 3.—Diagram demonstrating disseminated subendocardial necrosis involving inner shell of left ventricle; heart weight, 575 grams; moderate coronary arteriosclerosis and aortic stenosis; acute gastrointestinal hemorrhage.

greenish discolored areas. Occasionally areas simulating fatty change were present. The myocardial foci varied in size from discrete pinhead, rather well-delineated areas to wider and more irregularly-bordered flame-shaped zones.

Fig. 4.—Photograph of focal, disseminated, hemorrhagic areas of myonecrosis with predominant involvement of papillary muscles; heart weight, 350 grams; severe coronary arteriosclerosis; aortic stenosis; spontaneous attack.

TABLE I.   SITES OF MYOCARDIAL LESIONS (25 AUTOPSIES)

Anterior left ventricle	16
Posterior left ventricle	17
Interventricular septum	15
Anterior papillary muscle	20
Posterior papillary muscle	20
Right ventricle	4

Some averaged 5 to 10 mm. in diameter. In addition, broader, confluent areas of discoloration running parallel to the endocardial layer have been observed (Fig. 1). In some instances these had involved, either continuously or in skip fashion, a major part of the inner shell of the left ventricle (Figs. 2 and 3). Although the lesions were seen in any portion of the left ventricle, the papillary muscles disclosed abnormalities with somewhat greater frequency, particularly toward their apical segments (Table I). In some cases these regions were predominantly involved (Fig. 4). Indeed, these sites may be the only part affected

(Fig. 5).   Ischemic change of the right ventricle, including its septal portion, was uncommon.

The lesions which are the subject of this presentation have been restricted for the most part to the inner third of the wall of the left ventricle.   Occasionally in the more severely affected hearts, additional scattered ischemic foci were found within the middle third of the left ventricular wall, although never to the same degree as encountered just beneath the endocardium.   Involvement of the pericardium or subepicardial muscle zone was not observed.   Although the subendocardial musculature was characteristically involved, it should be pointed out that interposed between the endocardium and the affected portion there was often an apparently normal thin strip of muscle.   It is because of lack of change here, probably, that mural thrombi have been found so infrequently, and, when present, usually could be ascribed to antecedent myocardial disease.
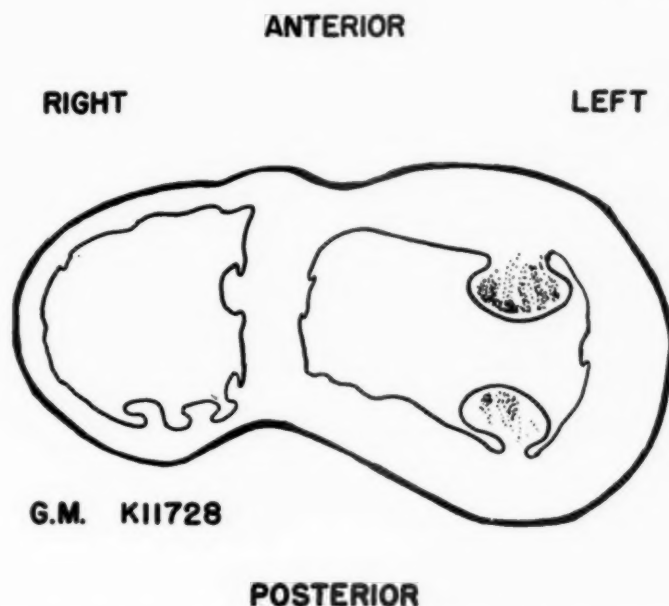

Fig. 5.—Diagram depicting sites of hemorrhagic necrosis confined to papillary muscles; heart weight, 575 grams; moderate arteriosclerosis; acute cardiac failure; uremia; hypertension.

It is significant that the ischemic myocardial foci have been irregularly disseminated.   The lesions, furthermore, have not been confined necessarily to the area of supply of the most severely narrowed vessel.   However, in an occasional case, the myocardium, in addition to the scattered zones, was the seat of a more confluent area corresponding to a severely stenotic arterial lumen.

The extent and severity of the myocardial alterations appeared to have varied with the duration and intensity of the predisposing and precipitating factors which are alluded to below.   It should be emphasized here that coronary insufficiency of transient or even fatal nature may occur without accompanying

morphological cardiac effects.   In the former, the episode of coronary insuffi-
ciency has been of such temporary or mild nature that compenstory forces have
prevented the development of anatomic change.   Evidently in the fatal instances
the patient had succumbed before the myocardium could develop any recogniz-
able lesion.   This is a feature which severe coronary insufficiency has in common
with attacks of acute coronary occlusion without any accompanying myocardial
infarction.

Fig. 6.—Photomicrograph of early ischemic lesion disclosing tinctorial changes, loss of nuclei of
myofibrils, slight focal hemorrhage, and reactive cellular infiltrate; normal muscle layer interposed be-
tween endocardium and affected area.   Same case as Fig. 3.

In the mild cases, lesions of the heart muscle were.detected only upon sys-
tematic histological examination.   These consisted of tinctorial alterations,
eosinophilic smudging, granularity or uneven staining of the affected myofibrils,
nuclear degeneration, loss of myostriations, foci of hemorrhage, and capillary
engorgement (Fig. 6).   The more advanced changes included widespread hemor-

Fig. 7.—Photomicrograph of posterior papillary muscle showing degeneration and homogenization of myofibrils, disappearance of nuclei, and widespread hemorrhage. Same case as Fig. 5.

Fig. 8.—Photomicrograph showing patchy subendocardial necrosis, focal interstitial hemorrhage, early polymorphonuclear leucocyte reaction. Same case as Fig. 3.

rhage, disappearance of nuclei, homogenization, vacuolization, and fragmenta-
tion of fibers (Fig. 7). Finally, there were focal or confluent zones of necrosis
with reactive infiltrates of polymorphonuclear leucocytes, lymphocytes, and
mesenchymal cells (Figs. 8, 9, 10, and 11). In older instances, granulation

Fig. 9.—Photomicrograph of section of left ventricle showing subendocardial capillary engorgement,
confluent linear foci of myocardial necrosis, hemorrhage, and conspicuous reactive polymorphonuclear
leucocyte infiltration; deeper myocardial layer normal; heart weight, 260 grams; severe arteriosclerosis
of the coronary arteries; paroxysmal auricular flutter.

tissue or cellular, edematous, richly capillarized connective tissue was present
(Fig. 12). The co-existence of recent organizing and healed foci has been a
common observation (Fig. 13). Presumably the older lesions represented the
sequelae of previous incidents of myocardial ischemia due to coronary insuf-
ficiency.

That the extent of involvement of the heart is quite variable is indicated by
the finding of seven instances of grossly visible necrosis of the major portion
of the left ventricular inner shell. In four hearts, on the other hand, lesions were

demonstrated only upon histological examination. This stresses the importance of diligent search. In this series examination of twenty-four hearts revealed acute ischemic alterations of the myocardium; one heart showed organizing lesions.

Fig. 10.—Photomicrograph of posterior papillary muscle revealing area of early necrosis with marked polymorphonuclear leucocyte reaction; heart weight, 570 grams; mild coronary arteriosclerosis; aortic and mitral stenosis; paroxysmal auricular tachycardia.
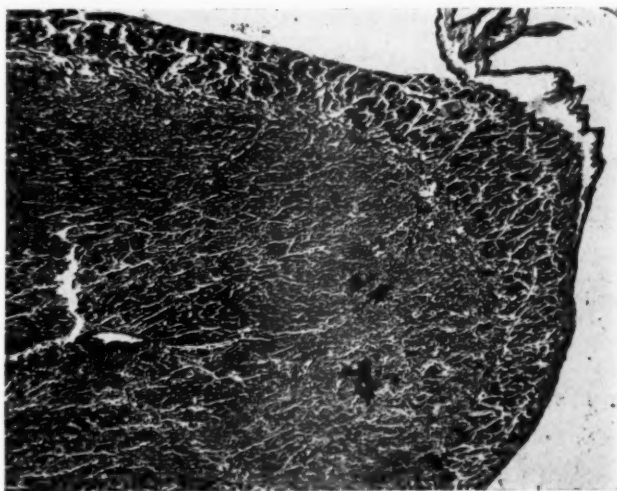
Fig. 11.—Photomicrograph of apex of posterior papillary muscle indicating area of severe necrosis, and multiple foci of hemorrhage surrounded by normal muscle. Same case as Fig. 4.

Attention is directed to the fact that the lesions described herein are more properly designated *necrosis* rather than *infarcts*. The latter term is restricted to denote a massive, sharply delineated area of necrosis secondary to an acutely occluded blood vessel.[2]

PREDISPOSING FACTORS OF ACUTE CORONARY INSUFFICIENCY

In general, any state which will impair the ability of the heart to make necessary and adequate compensations in coronary flow will render the myocardium susceptible to bouts of acute coronary insufficiency. Stenosis of the coronary artery lumen produced by arteriosclerotic intimal plaques and narrowing of the coronary ostia due to syphilis or arteriosclerosis of the aorta will produce a permanent increase in resistance to coronary blood flow. Valvular lesions such as aortic stenosis and often aortic insufficiency decrease the effective aortic perfusion pressure and coronary blood flow.[6] Cardiac hypertrophy in itself augments requirements for myocardial blood supply.[7]
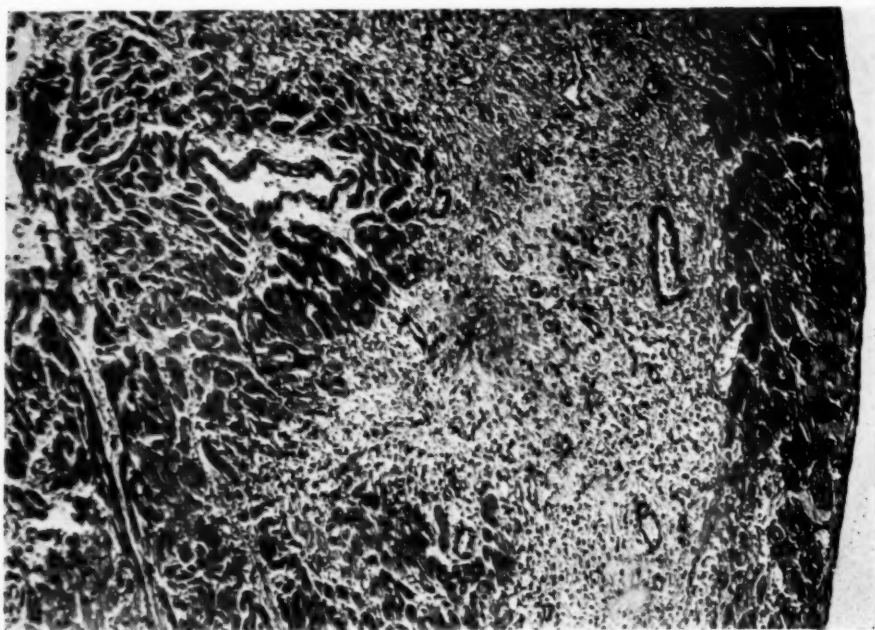

Fig. 12.—Photomicrograph of posterior wall of the left ventricle, disclosing swelling, rarefaction of subendocardial myofibrils, confluent areas of granulation tissue (organizing necrosis); heart weight, 400 grams; severe coronary arteriosclerosis; bleeding gastric ulcer.

In a similar manner, one may consider such nonstructural conditions as chronic anemia and chronic congestive failure. In the former, the increased cardiac output accompanying this condition[8] may not be enough to compensate for the decreased oxygenation of the blood and thus predispose to the intensification of coronary insufficiency. In chronic heart failure the cardiac output becomes insufficient for tissue needs, including that of the myocardium.[9]

Despite the importance of these considerations, it is to be noted that even in a normal heart myocardial ischemia may be produced by acute coronary insufficiency. Nevertheless, hearts with intrinsic disease are decidedly more vulnerable to sudden alterations of coronary blood flow. Accordingly, the aforementioned anatomical abnormalities have been termed predisposing factors for coronary insufficiency.[4]

Arteriosclerosis of the coronary artery tree with moderate or severe narrowing of the lumen was common in our series (Table II).   Of the twenty-five hearts studied, there were nineteen with coronary arteriosclerosis with moderate to severe stenosis of the lumen.   In the remaining six hearts the arterial involvement was either absent or minimal.   It appeared, generally, that the more severe the arterial disease, the more widely distributed and pronounced were the muscle changes.   In seven hearts showing extensive involvement of the inner shell of the left ventricle there was severe arteriosclerosis of the coronary arteries with stenosis of the lumen.   It is to be emphasized that in no instance was a recent occlusion of a coronary artery found, despite detailed search.   In one case moderate intimal hemorrhage was noted but was considered of insufficient degree to have been a factor in narrowing of the lumen and in the appearance of the myocardial lesions.
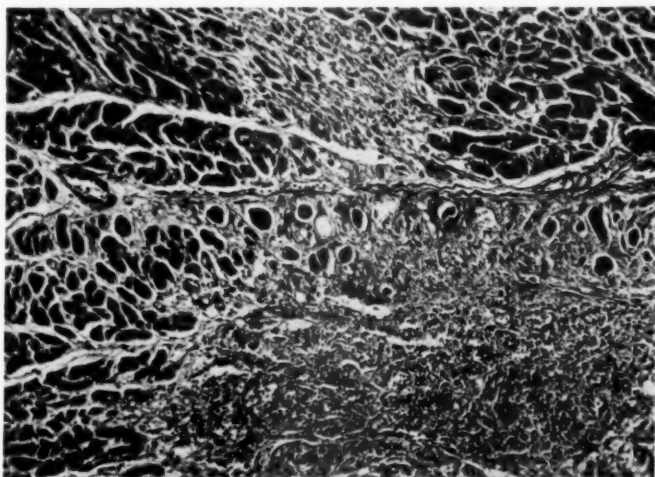

Fig. 13.—Photomicrograph of the posterior wall of the left ventricle, showing coexistence of recent and organizing foci of myocardial necrosis, reactive cellular infiltrate, and focal hemorrhage; heart weight, 300 grams; moderate coronary arteriosclerosis; recurrent pulmonary embolism.

Hypertrophy was encountered in twenty-two of the twenty-five hearts, the weights ranging from 350 to 600 grams.   The factor of enlargement becomes especially important in light of the fact that the cardiac capillary network per unit of myofibril decreases with the expansion of the muscle mass no matter what its cause.[10]   The disparity between the progressively enlarging heart and its capillary bed contributes to myocardial ischemia.   In addition, the thickness of the muscle fiber in a large heart militates against proper oxygen diffusion, for Harrison and his co-workers have demonstrated that the thicker the cardiac muscle fiber, the longer is the time required for metabolic exchange.[11]   Not only does the increased muscle mass require more blood flow for its nutrition, but the increased work necessary to overcome hypertension, a valvular defect, or coronary stenosis also augments the consumption of oxygen.[7]   An increase in size, length, tortuosity of the primary coronary arteries in enlarged hearts,

TABLE II. PREDISPOSING CARDIAC LESIONS (25 AUTOPSIES)

Coronary arteriosclerosis	
Severe	14
Moderate	5
Mild or none	6
Hypertrophy of heart	22
Valvular lesions	
Aortic stenosis (rheumatic)	5
Mitral stenosis (rheumatic)	1
Aortic insufficiency (syphilitic)	1

and rich collateral arterial anastomoses in arteriosclerotic heart disease have been reported.[12-14] Despite these compensatory features, advancing coronary artery narrowing or valvular disease and an enlarging cardiac muscle mass conspire ultimately to impair myocardial nutrition.

It is significant that some of the most striking acute myocardial alterations in the present series were found in the hypertrophied hearts accompanying stenosis of the aortic valve. Conspicuous lesions of the leaflets and ring of the aortic and mitral valves were noted seven times. These included five cases of fibrocalcific aortic stenosis, one case of mitral stenosis, and one case of syphilitic aortitis with valvular deficiency and narrowing of the coronary ostia.

PRECIPITATING FACTORS OF ACUTE CORONARY INSUFFICIENCY

Since an acute coronary occlusion was not present in any of the hearts studied, other factors must have operated to have induced severe acute ischemia of the heart muscle.

A group of patients with underlying cardiac disease—four in this series—developed episodes of coronary insufficiency in the absence of any manifest precipitating causes as indicated below. Apparently in these cases the coronary arteriosclerosis, valvular disease, or cardiac hypertrophy had reached such a point in its development that the coronary blood flow, even under basal conditions, became inadequate despite the patients' usual level of cardiac output and relatively effective aortic perfusion pressure. The presence of myocardial fibrosis incident to valvular disease, coronary artery stenosis, or previous coronary artery occlusion had not only decreased the cardiac reserve but also had made the heart muscle less resistant to ischemia. Consequently it appears that slowly progressive coronary arteriosclerosis and valvular deformity can so compromise cardiac nutrition that morphologic myocardial changes may result from the spontaneous failure of compensatory mechanisms.[2]

No discussion of acute coronary insufficiency can be complete without a consideration of factors which may act as precipitating agents (Table III). In the series described herein there were five instances each of acute cardiac failure and of tachycardia. It is believed that these acted as primary precipitating forces by inducing or intensifying any existent myocardial ischemia, although it is appreciated that both cardiac failure and a rapid ventricular rate often result from deficient coronary artery blood flow. In four instances, myocardial necrosis

was precipitated by acute hemorrhage, in two additional cases by hemorrhagic dissection of the aorta, in three instances it followed pulmonary embolism, in one it was due to postoperative shock, and in one it followed severe infection.   In the four "spontaneous" cases cited above, no competent initiating extracardiac mechanism was detected.   In acute cardiac failure there is almost always an alteration in cardiac output[9] which results in inadequate coronary blood flow.   Although marked tachycardia may temporarily increase cardiac output, it further augments the work of the heart.   The greater expenditure of energy coupled with an increased nutritional demand of the cardiac muscle necessitated by the rapid rate and the shortening of the diastolic rest period ultimately combine to reduce coronary blood flow.[15]

TABLE III.   PRECIPITATING FACTORS (25 AUTOPSIES)

Acute heart failure	5
Tachycardia	5
Spontaneous	4
Hemorrhage	4
Pulmonary embolism	3
Dissecting aneurysm	2
Postoperative shock	1
Infection, severe	1
Total	25

The course of events in acute hemorrhage may be considered.[16]   Moderate bleeding decreases the venous return to the heart, circulating blood volume, cardiac output, and arterial blood pressure.   The resultant lowered aortic perfusion pressure leads to a diminution in coronary blood flow.   However, compensatory mechanisms are brought into play almost immediately.   Reflexly, the heart rate increases and peripheral vasoconstriction ensues.   Consequently, the blood pressure may revert to normal and even an actual increase in cardiac output often occurs, so that coronary flow will be maintained adequately.   Restoration of blood volume may be accomplished further by the transfer of interstitial fluid into the circulating blood stream.   With severe, untreated hemorrhage, manifestations of shock soon appear. Vasoconstriction may be so intense or prolonged as to reduce blood flow to the tissues throughout the body. On the other hand, this compensating vasoconstriction is easily exhausted, so that blood pressure falls and remains at low levels.   Fluid transfer into the vascular tree may produce hemodilution and a further decrease in hemoglobin concentration.   It has been suggested that the coronary arteries participate in the generalized vasoconstriction and so enhance myocardial ischemia.   As the compensatory mechanisms fail, the coronary blood flow is diminished.   An uncompensated deficient coronary blood flow leads to relative ischemia of heart muscle, and the more vulnerable ventricular areas undergo functional and subsequently irreversible anatomical alterations.   In the presence of aortic stenosis, particularly when accompanied by arteriosclerotic narrowing of the coronary lumen, acute hemorrhage has been found to produce marked myocardial effects. It is recognized that hypertrophied hearts secondary to aortic lesions, notably

aortic stenosis, are in a state of chronic myocardial ischemia, probably the result of small cardiac output and increased coronary resistance. The decrease in aortic perfusion pressure by acute hemorrhage in turn intensifies the already diminished coronary flow and often has led to striking subendocardial necrosis.[16]
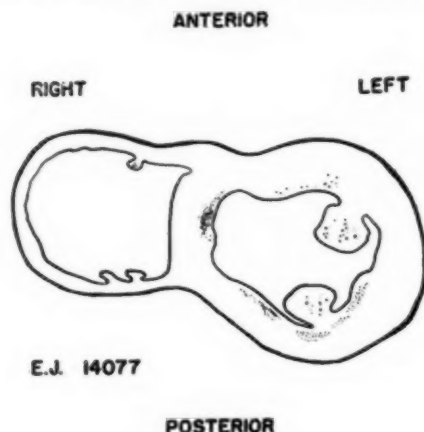

Fig. 14.—Diagram illustrating location of subendocardial necrosis with widespread involvement of the left ventricle; focal areas in anterior papillary muscle of right ventricle. Same case as Fig. 13.

Shock is a most important factor in the production of coronary insufficiency, whether it is due to blood loss, trauma, or operation. The abrupt fall in cardiac output and blood pressure due to diminution in circulating blood volume and in venous return to the heart rapidly leads to decreased coronary flow. Corday and his associates[17] have demonstrated that in experimental animals with partial coronary ligation, a diminution or loss of contractility occurs, and the entire heart, especially the ischemic region, becomes cyanotic when blood pressure is lowered. In dissecting aneurysm of the aorta, the factors of shock and subsequent hemorrhage are operative. Acute coronary insufficiency, furthermore, may develop in patients who have sustained embolization of the pulmonary artery[18-20] and may produce acute lesions of both right and left ventricles (Fig. 14). An analysis of the three cases included in this presentation and others previously described indicates that ischemia induced by diminished aortic pressure secondary to shock constitutes but one basis for the myocardial abnormalities. Additional considerations include recurrent episodes of embolization, with repeated reductions of blood pressure over a prolonged period. The anoxia attending such incidents arises from the diminished pulmonary blood flow and impaired oxygenation of blood. This, plus the right ventricular dilatation and possible reflex coronary vasoconstriction, all combine to induce deleterious cardiac effects. Moreover, these factors are even more prone to produce such consequences in patients with antecedent heart disease.

COMMENT

The reason for the localization of the lesions to the subendocardial muscle and papillary muscles is still a subject for speculation. When we first presented

a study of this subject in 1939 it was believed that such localization was due to the fact that the affected areas were remote from the source of blood supply.[2] However, other conditions may be more directly responsible.   The relatively greater degree of work imposed upon the papillary muscles by systolic contraction of the ventricle plus tension exerted upon the mitral valve appears to be an additional reason for increased nutritional demand.   Another factor which may account for the predominantly subendocardial ischemia is that the epicardial portion of the left ventricular myocardium has a richer collateral blood supply than the endocardial side.[21]

Further, it has been shown that during systolic contraction the gradient of intramyocardial pressure diminishes from the deeper to the more superficial layers of the cardiac wall.[22]   The intramural pressure in the depth of the myocardium exceeds that of the aortic pressure, while in the superficial zones it may be equal to or even less than the pressure within the aorta and coronary artery tree.   Accordingly, increased pressure is exerted against the susceptible areas during isometric cardiac contractions, and it is likely, therefore, that the zones which require a greater oxygen supply react more profoundly to oxygen deprivation.   The preponderance of left ventricular lesions as contrasted to involvement of the right ventricle may be accounted for by the relatively less efficient Thebesian circulation in ratio to the proportionately greater muscle mass of the left over that of the right ventricle.

TABLE IV.   HEART WEIGHT AND CORONARY SCLEROSIS (25 AUTOPSIES)

	AVERAGE HEART WEIGHT (GM.)	DEGREE OF CORONARY ARTERIOSCLEROSIS		
		MILD	MODERATE	SEVERE
Cardiac failure	547	1	1	3
Tachycardia	410	2	..	3
Spontaneous	396	..	..	4
Hemorrhage, acute	412	2	1	1
Pulmonary embolism	348	1	2	..
Dissecting aneurysm	435	..	1	1
Postoperative shock	466	..	..	1
Infection, severe	430	..	1	..

It is necessary to re-emphasize that not only may an enlarged heart with stenotic coronary vessels be subject to spontaneous episodes of acute and chronic coronary insufficiency with or without myocardial necrosis, but also that such hearts often may develop acute coronary insufficiency due to certain precipitating factors (Table IV).   Shock, hemorrhage, and tachycardia, for example, are matters of especially deep concern and gravity in patients with cardiac abnormalities.

It is pertinent to inquire whether or not it is preferable for the clinician, when considering coronary disease, to stress the anatomical myocardial lesions and to minimize the importance of the physiological mechanisms involved in their production.

Acute diseases of the coronary arteries have been divided into the following three categories: (1) angina pectoris, or chest pain of transitory nature; (2) "coronary failure," or chest pain lasting twenty minutes or more without clinical or anatomical evidence of myocardial necrosis; and (3) myocardial infarction with or without acute coronary occlusion.[23]

This subdivision seems to us confusing. Certainly patients in the first two groups have been seen with or without myocardial necrosis. It appears more accurate and practical to attempt to define the manifestations of coronary artery disease as *due to* either acute coronary insufficiency or acute coronary occlusion, thus approaching the problem physiologically in terms of a precipitating cause, dynamic pathology, and diagnosis. This can be accomplished usually on the basis of certain clinical and electrocardiographic features.[4] In the former the clinical manifestations are due to dysfunctional insufficiency of coronary flow, while in the latter they are the result of an acute organic obstruction of a coronary artery. It is essential, moreover, to recall that the ischemia due to acute coronary insufficiency may not progress to actual necrosis, but, if it does, it is generally patchy in character. Certainly the subendocardial lesion following shock, hemorrhage, or persistent tachycardia is not equivalent to the massive, well-circumscribed infarct due to an acute coronary occlusion. Clinically and anatomically, then, there are well-marked differences. The method of therapy, furthermore, is dependent upon the accurate differentiation and evaluation of these two conditions.[24]

It is to be emphasized that when the presence of a massive infarct due to recent coronary occlusion can be excluded clinically, and one is left with the possibility of acute coronary insufficiency, an attempt must be made to determine the nature of the initiating physio-pathological factor. The clinical diagnosis must be qualified by the designation of the type of physiological abnormality which may be operative. The efficacy of treatment in acute coronary insufficiency depends to a great extent upon the mechanism involved. When a precipitating factor cannot be detected, the episode of coronary insufficiency must be assumed to represent the spontaneous variety due to progressively advancing intrinsic cardiac disease. It must also be recognized that occasionally a rapidly developing intimal hematoma may induce a bout of acute coronary insufficiency and so may represent the premonitory phase of an acute coronary artery occlusion.[5,25,26]

SUMMARY

1. A series of twenty-five cases is presented in which recent myocardial change was found in the absence of acute coronary occlusion.

2. The lesions were confined for the most part to the subendocardial musculature and the papillary muscles of the left ventricle. They varied in extent from a few scattered microscopic foci to widespread disseminated and grossly visible areas. In seven instances almost the entire inner shell of the left ventricle was involved. The possible reasons for the localization of the lesions are considered.

3. The mildest changes consisted of eosinophilic smudging; granularity, uneven staining, and loss of striations of the affected myofibrils; nuclear de-

generation; areas of hemorrhage and capillary engorgement.   More advanced lesions showed widespread hemorrhage; disappearance of nuclei; homogenization, vacuolization, rupture of muscle fiber; and finally, focal or confluent zones of necrosis with reactive infiltration by polymorphonuclear leucocytes, lymphocytes, and mesenchymal cells.   Granulation and fibrous tissue characterized the older lesions.

4.   Examination of twenty-four hearts disclosed acute ischemic changes; one showed organizing lesions only.   These alterations are believed to have been caused by intense myocardial ischemia due to acute coronary insufficiency.

5.   Coronary arteriosclerosis with moderate or severe narrowing was present in nineteen cases.   Twenty-two hearts were hypertrophied.   Six hearts, in addition, revealed extensive fibrocalcific aortic stenosis; one had mitral stenosis; one had syphilitic aortitis with aortic insufficiency and coronary ostial stenosis. Myocardial ischemia may be produced by acute coronary insufficiency, even in a normal heart.   However, hearts with intrinsic diseases (predisposing factors) are much more vulnerable than normal hearts.

6.   A variety of factors appeared to have precipitated a state of acute coronary insufficiency.   These consisted of tachycardia, acute heart failure, acute hemorrhage, pulmonary embolism, dissecting aortic aneurysm, postoperative shock, and severe infection.   In four instances no such initiating mechanism was detected.

7.   The inter-relationships between the predisposing and precipitating factors are discussed.

8.   Coronary insufficiency is usually precipitated by a physio-pathological mechanism.   The clinical recognition of such factor is essential to the accurate differentiation of acute coronary insufficiency from acute coronary artery occlusion and for the definitive therapy of the patient.

9.   Where a precipitating factor for the appearance of coronary insufficiency is not detectable, the clinical episode is diagnostic of progressively advancing intrinsic cardiac disease.

10.   The preferred terminology in conditions involving acute myocardial ischemia is one that divides acute coronary insufficiency from acute coronary occlusion.   This is preferred by virtue of priority and clarity of definition.

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THE EFFECT OF POTASSIUM ON INVERTED T WAVES IN ORGANIC HEART DISEASE

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THE effects of hyper- and hypopotassemia on the electrocardiogram have been well established in numerous clinical conditions such as uremia, Addison's disease, shock, intestinal obstruction, crush syndrome, infantile diarrheas, transfusion reactions, diabetic acidosis, and familial periodic paralysis, and these effects have been carefully cataloged in the experimental animal.[1-22] However, there are but few reports on the effects of induced hyperkalemia on the T waves in patients with abnormal electrocardiograms due to organic heart disease.

Sharpey-Schafer[21] demonstrated that the administration of potassium salts accentuated the inverted T waves in myocardial infarction, while in left ventricular preponderance the inverted T waves were returned to normal by induced hyperpotassemia. Also, he was able to produce an upright from an inverted T wave in hypothyroidism within two hours after the administration of potassium salts, a result similar to that caused by thyroid hormone over a longer period of time.[24] The administration of 12.5 Gm. of potassium chloride caused inverted T waves to become upright in Leads I and IV in a patient with severe hypertensive cardiovascular disease.[25] Bryant[25] gave oral potassium salts on twenty-five occasions to patients with hypertensive cardiovascular disease, and in most instances the inverted T waves became less inverted or upright, and the upright T waves became more positive. Also, he found that sodium restriction in this type of case produced electrocardiographic changes similar to those of increased potassium ingestion.

Recently it has been reported that inverted T waves occurring in precordial leads taken over the right ventricle, which are of functional origin, can become normal by the ingestion of a mixture of potassium salts. It was postulated that these inverted T waves were due to the fact that the right ventricle normally contains less potassium than the left.[27] However, it does not follow that, because potassium causes an inverted T wave to become upright, this is due to a lack of potassium. Many drugs which are not a normal constituent of the myocardial milieu (atropine, nitroglycerine, ergotamine) may restore inverted T waves to an upright position.

The importance of potassium for the normal cardiac action was demonstrated originally by Ringer[28] when he produced cardiac standstill in diastole, with an excess of the potassium ion. Osterhout and Hill,[29] in experiments with the

TABLE

NAME	AGE	DIAGNOSIS	CONTROL			15 MINUTES		
			I	CF₅	K	I	CF₅	K
JW	50	Hypertension	I	I	3.1			
JM*	50	Aortic regurgitation	I	I	3.9			
FU	58	Hypertension	I	I				
PT	82	Hypertension	I	I	2.7			
BK	76	Hypertension	I	I	3.1			
BM	50	Coronary thrombosis	I	I	3.3			
JW	49	Hypertension	I	D	3.3			
MN	90	Hypertension	I	D	4.1			
RB	46	Hypertension	I	I	2.6			
PK	72	Hypertension	U	I	3.3			
LK	80	Hypertension	I	I	4.1			
RK	58	Hypertension	I	I	3.7			
CW	68	Hypertension	I	I	5.0			
RS	43	Hypertension	I	I	5.8			
MP	76	Hypertension	I	I	6.8			
MC	86	Hypertension	I	I	4.8			
JP	89	Hypertension	I	I	5.0			
FC	61	Hypertension	I	I				
AF†	76	Hypertension	I	I	5.4	0	0	5.9
BT	82	Hypertension	I	I		0	0	
CB	75	Hypertension	I	I		0	0	
DM‡	71	Hypertension	I	I	4.3	0	0	5.3
EB	57		I	I	4.0	0	U	4.1
HA	62	Hypertension	I	I	5.2	0	0	6.5
BB§	77	Hypertension	D	I	5.1			
HP‖	65	Coronary thrombosis	U	I	6.6	+U	U	6.8
AP	63	Coronary thrombosis	I	I	5.9	0	0	5.5
RH	57	Coronary thrombosis	D	U		0	0	
JS	73	Coronary thrombosis	I	I		0	0	
JC¶	37	Hypertension	D	U	4.3	U	+U	4.6
AB	48	Hypertension	I	I	4.1	0	0	5.6

*JM Developed an uprighting of inverted T waves in Leads II and III.
†AF Developed a Wenckebach block within thirty minutes of potassium ingestion.
‡DM T waves in Lead II became significantly taller in forty-five minutes after potassium.
§BB T waves became more deeply inverted in Lead CF₅.
‖HP Inverted T waves in Lead III became upright and those in Lead II much taller.
¶JC Developed an A-V nodal rhythm sixty minutes after ingestion of the potassium.
KEY

O= no change.
I= inverted.
U= upright.
D= diphasic.

+U= increase in uprighting.
++U= further increase in uprighting.
−I= decrease in inversion.
+I= increase in inversion.

Nitella flexelis cell, demonstrated that potassium chloride, applied locally, caused a depolarization and could act as a pacemaker for the initiation and rhythmic production of action currents. In recent experiments, when cats' hearts were made ischemic, there was a 50 per cent increase in the potassium content of the coronary venous blood.[30] Also, patients dying of heart failure may show a diminution in the myocardial potassium.[31] It has been shown that overwork and strain cause a loss of cardiac potassium. In fact, in patients dying of chronic fibrotic lung disease, the right ventricle may show a potassium deple-

I.

30 MINUTES			60 MINTUES			90 MINUTES			REACTIONS	K DOSE
I	CF₅	K	I	CF₅	K	I	CF₅	K		
			U	U	4.1				Headache	5 Gm.
0	0		0	0	4.1				Nausea	5 Gm.
0	0		0	0					Sweating	5 Gm.
0	0		0	0	3.3				None	5 Gm.
0	0		0	0	3.3				None	5 Gm.
0	0		0	0	3.6				None	5 Gm.
0	U	3.5	0	D	3.8				Sweating	8 Gm.
0	U	4.1	0	D	3.6				None	8 Gm.
0	0	3.1	0	0	3.0				None	10 Gm.
+U	−I	3.3	++U	U	3.8				None	12 Gm.
0	0	4.0	0	0	4.8				None	15 Gm.
0	0	4.8	0	0	4.4	0	0	7.4	None	15 Gm.
0	0	6.4	0	0	6.8	0	0	8.2	None	15 Gm.
0	0	9.0	0	0	8.8	0	0	9.4	None	15 Gm.
0	0	6.8	0	0	7.8	0	0		None	15 Gm.
0	0	6.4	0	0	6.4	0	0	7.2	None	15 Gm.
0	0	5.6	0	0	7.7	0	0	8.0	Nausea; vomited	12 Gm.
0	0		0	0		0	0		None	12 Gm.
0	0	6.0	0	0	6.3				None	12 Gm.
0	0		0	0		0	0		None	12 Gm.
0	0		0	0		0	0		None	12 Gm.
0	0	5.9	0	0		0	0	6.7	None	12 Gm.
			0	U	4.4				None	12 Gm.
0	0	6.3	0	0	5.5				Vomited	8 Gm.
0	+I	5.8	0	+I	6.5				Nausea	12 Gm.
+U	U	8.0	+U	++U	8.5				None	16 Gm.
0	0	5.7	0	0	6.5				Nausea	16 Gm.
U	+U		U	+U					None	16 Gm.
0	0		0	0					None	16 Gm.
U	+U	4.8	U	+U	4.6				None	16 Gm.
0	0	5.8	0	0	6.1				None	16 Gm.

tion greater than the left ventricle.[31]   The suggestion has been made that the alterations of the electrocardiogram in acute coronary thrombosis may be due, in part, to alteration in the local level of potassium in the heart muscle.[30]

MATERIAL AND METHODS

Thirty-one patients who were hospitalized for cardiovascular conditions and whose electrocardiograms showed the pattern of a left ventricular hypertrophy or a myocardial infarct were the subjects for this study.   Control electrocardiograms and serum potassium levels were taken.   The patients then received
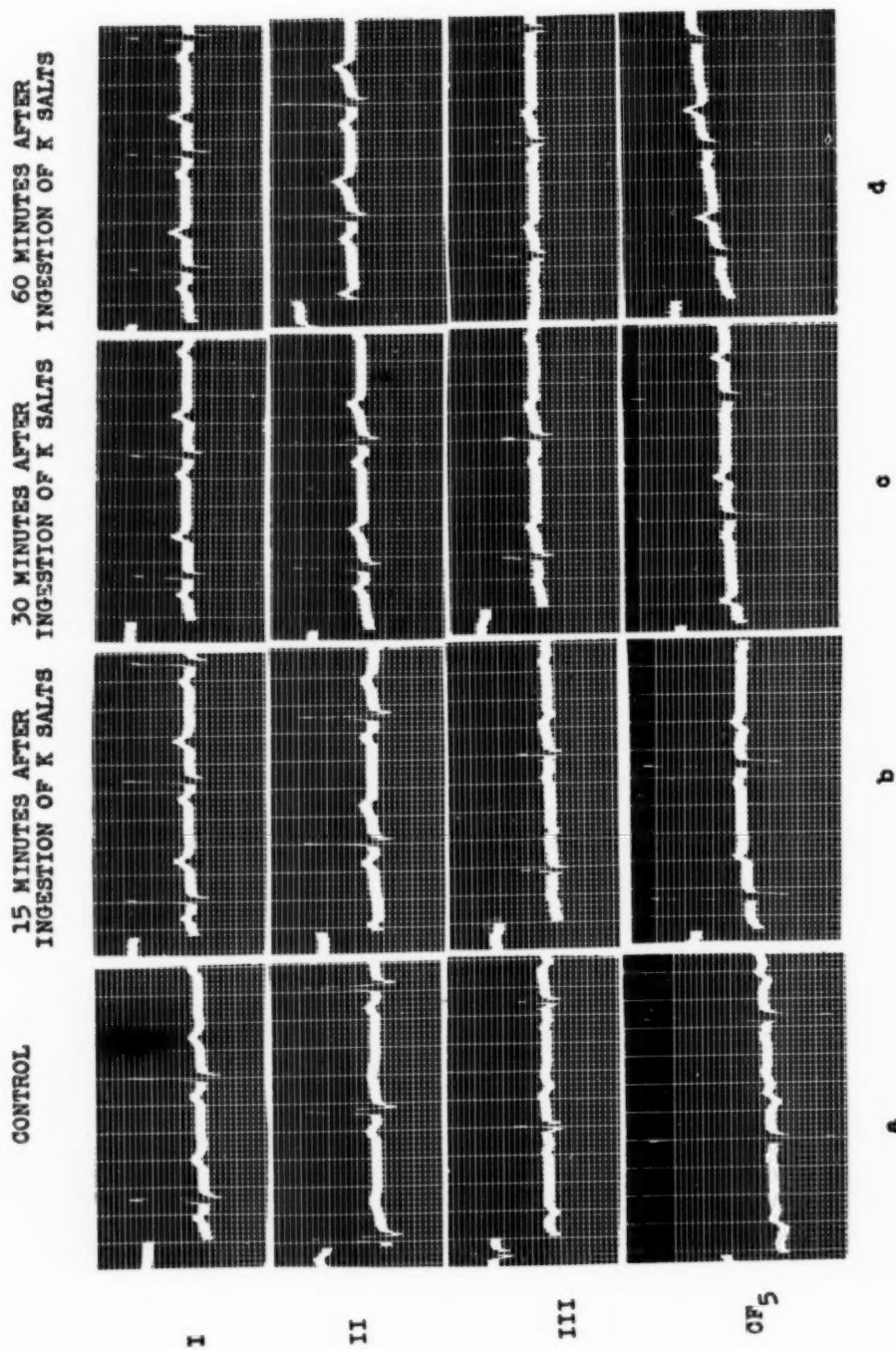
Fig. 1.—*a*, Control. *b*, This was recorded fifteen minutes after the ingestion of 16 Gm. of potassium salts. The T waves in Leads I and II are much taller and those in Leads III and CF₅ have changed from being inverted to diphasic. *c* and *d*. At the thirty- and sixty-minute periods, the T waves in Leads I and II have become still taller and those in Leads III and CF₅ are now definitely upright.

orally from 5 to 16 Gm. of a mixture of potassium chloride, potassium citrate and potassium bicarbonate in a 25 per cent solution, one dram of the mixture equalling one gram of the salt.   Electrocardiograms and serum potassium levels were determined at 15-, 30-, 60-, and 90-minute intervals.   The serum potassium estimations were done by the flame photometer method using a modification of the Barnes, Richardson, Berry, and Hand technique.[33]   A normal serum potassium level by this method is from 3.5 to 4.5 millequivalents.

RESULTS

Nine of the thirty-one patients studied showed significant alterations in the T waves after the administration of potassium salts (Table I).   These consisted of change to the upright of inverted or diphasic T waves, or a significant decrease in the inversion.   One patient developed a Wenckebach block thirty minutes after the ingestion of the potassium mixture, and this persisted for 120 minutes. In one patient, the rhythm changed from a sinoauricular to an auriculoventricular nodal rhythm within sixty minutes after the ingestion of the potassium salt mixture.   No significant alteration occurred in the QRS complexes, R-ST segments, or in the P waves.   The potassium salts caused no alarming reactions, although seven patients complained of either nausea, excessive perspiration, or vomiting.

Fig. 1,*a* is the control tracing of a 65-year-old man.   This was taken five weeks after he was admitted to the hospital because of severe substernal pain with radiation into the left arm of several hours' duration.   A similar episode had occurred one week previously. Serial electrocardiograms revealed an acute anteroseptal myocardial infarct and the history indicated a long-standing hypertension. He received 16 Gm. of potassium salts and Fig. 1,*b* was recorded fifteen minutes later.   This shows that the T waves in Leads I and II are much taller, and those in Leads III and CF_5 have changed from an inverted to a diphasic character. Thirty and sixty minutes after the ingestion of potassium salts, the T waves in Leads I and II have become still taller and those in Leads III and CF_5 are now definitely upright.   The serum potassium levels ranged from the control level of 6.6 meq. to 6.8 in fifteen minutes, 8.0 in thirty minutes, and 8.5 in sixty minutes.

Fig. 2,*a* shows the serial tracings of a 57-year-old man who was diagnosed as having an acute anteroseptal myocardial infarct with possible involvement of the posteroseptal area.   Leads I and CF_5 are indicative of a left ventricular hypertrophy.   The upright T waves in CF_5 on Jan. 5, 1950, were considered to be a trend to the normal of previously inverted waves produced by the acute myocardial infarction.

Fig. 2,*b* is the control tracing taken approximately two months after the acute myocardial infarction.   The patient received 12 Gm. of potassium salts, and Fig. 2,*c*, taken fifteen minutes later, shows that the T waves in Lead CF_5 have now become upright.   Forty-five minutes later, the T waves in Lead CF_5 have reverted to the control configuration.   No significant alterations occurred
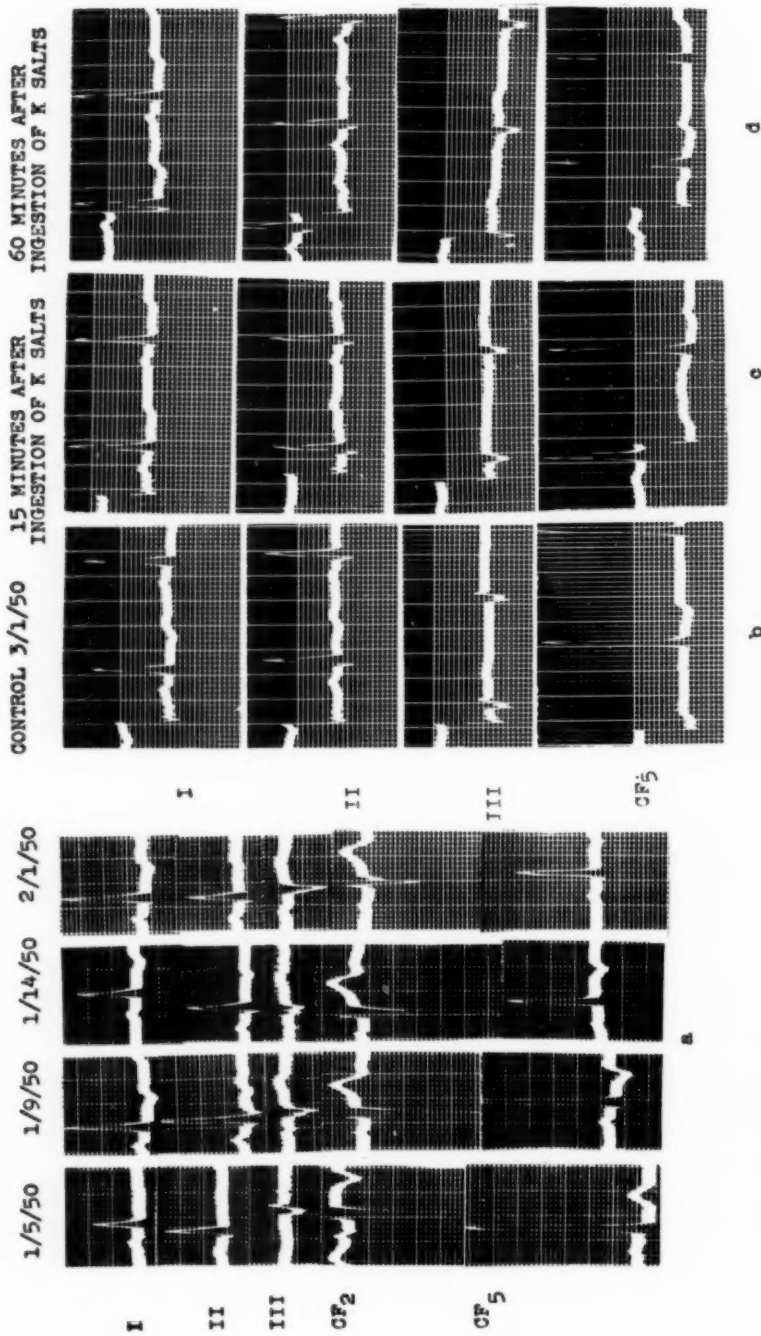
Fig. 2.—These are serial tracings which were interpreted as caused by an acute anteroseptal myocardial infarct with possible involvement of the posteroseptal area. Leads I and CF₅ are indicative of a left ventricular hypertrophy. The patient received 12 Gm. of potassium salts approximately two months after the acute myocardial infarct and Fig. 2,c taken fifteen minutes after ingestion, shows that the T waves in Lead CF₅ have now become upright.

in the other leads.   The control serum potassium was 4.0 meq.; the serum potassium was 4.1 meq. at fifteen minutes and 4.4. meq. at the end of sixty minutes. This cannot be considered a significant rise in the serum potassium level.
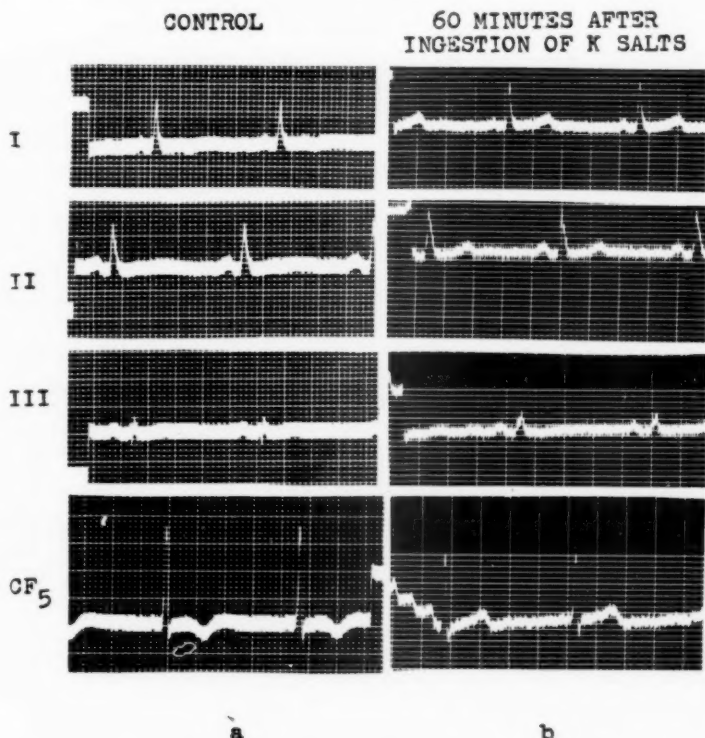

Fig. 3.—*a*, Control.   *b*, This was recorded one hour after the ingestion of 5 Gm. of potassium salts. This shows that the flatly inverted T waves in Lead I have become definitely upright and those in Lead II more positive.   The inverted T waves in Lead CF₅ also have become upright.

Fig. 3,*a* is the control tracing of a 50-year-old man who was admitted to the hospital for diabetes mellitus and hypertensive cardiovascular disease.   He received 5 Gm. of potassium salt and Fig. 3,*b* was recorded one hour later.   This shows that the inverted T waves in Lead I have become definitely upright and those in Lead II have become more so.   The cove-shaped inverted T waves in Lead CF_5 also have become upright.   The control serum potassium was 3.1 meq., and one hour later it was 4.1 meq.   Although the potassium dose was comparatively small and the rise in the serum potassium level of minor magnitude, the electrocardiographic changes were quite definite.

Fig. 4,*a* is the control tracing of a 72-year-old man with left ventricular failure and a blood pressure of 210/140 mm. Hg.   This tracing reveals flat T waves in Lead I, slurred, widened Q waves in Lead III, and inverted T waves in Lead CF_5.   The patient received 8 Gm. of potassium salts and thirty minutes later (Fig. 4,*b*) the T waves in Lead I became more positive and those in Lead CF_5 diphasic.   Sixty minutes after the ingestion of the potassium salts, the T waves in Lead I were definitely more upright and also the T waves in Lead CF_5

had become upright (Fig. 4,*c*).   The control serum potassium was **3.3** meq. and the same at the thirty-minute interval.   At sixty minutes the potassium level had risen slightly to 3.8 meq.
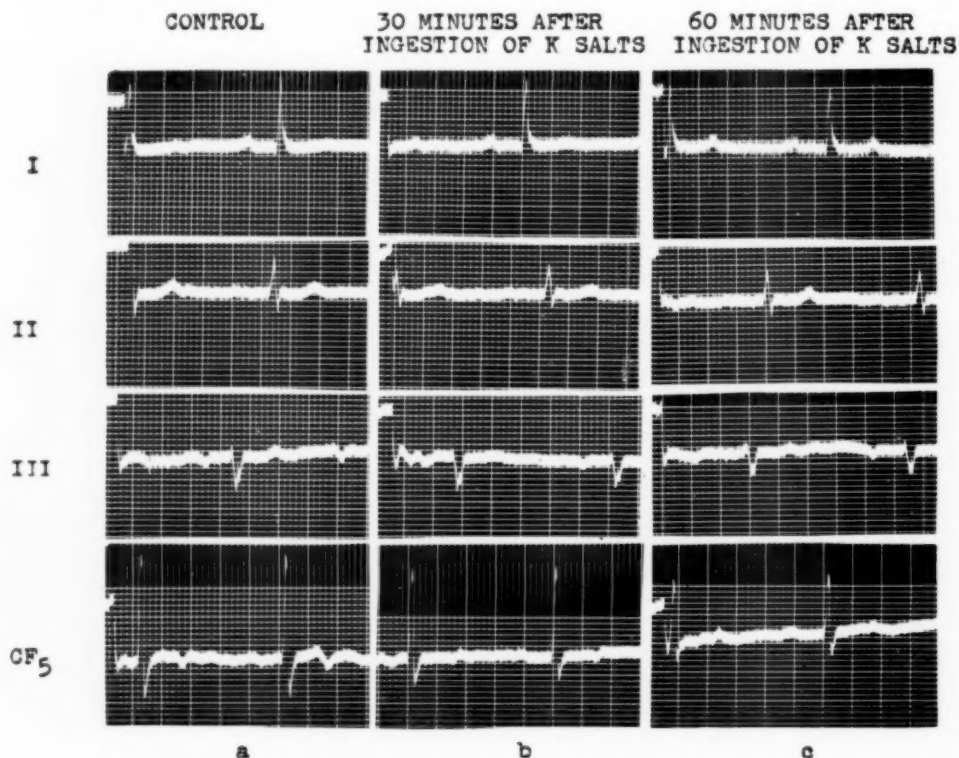

Fig. 4.—*a*. Control.   *b*, This was taken thirty minutes after the ingestion of 8 Gm. of potassium salts. It reveals that the T_1 is more upright and that the T waves in Lead CF_5 have changed from being inverted to being diphasic.   *c*. Thirty minutes later T_1 is even more upright and T_{CF_5} also has become definitely positive.

Fig. 5,*a* is the control electrocardiogram of a 49-year-old man who was hospitalized for left ventricular failure and high blood pressure.   This tracing is typical for a left ventricular preponderance with inverted T waves in Leads I and II and diphasic T waves in Lead CF_5, depression of the R-ST segments in Leads I and II and especially in Lead CF_5.   Thirty minutes after the ingestion of 5 Gm. of potassium salts the T waves in Lead CF_5 became upright and the R-ST segments showed slightly less depression.   The T waves were peaked with a narrow base characteristic of hyperpotassemia (Fig. 5,*b*).   The T waves reverted to their control contour at the sixty-minute interval (Fig. 5,*c*).   No significant alterations occurred in the other leads except that the T waves were slightly narrower in Lead CF_2 thirty minutes after the administration of the potassium salts.   The control serum potassium level was 3.3 meq. and in thirty minutes, when significant electrocardiographic changes took place, the serum potassium was 3.5 meq.   At sixty minutes, when the electrocardiogram had reverted to control position, the serum potassium was 3.8 meq.

DISCUSSION

Many authors state that there is a definite correlation between the height of the T waves and the concentration of serum potassium and that the electrocardiographic changes follow a definite sequence, depending on the level of the serum potassium.[18,22,13]   At a concentration of 5 to 7.8 meq. there is an increase
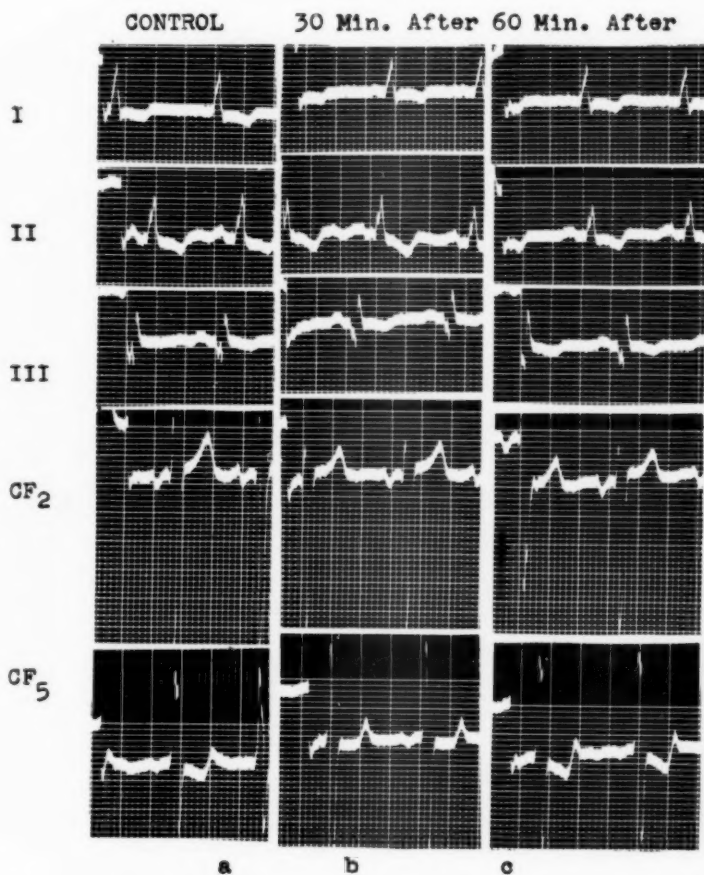

Fig. 5.—*a*, Control. *b*, This was recorded thirty minutes after the ingestion of potassium salts.   It reveals that the diphasic T waves in CF_5 have become definitely upright. *c*, Sixty minutes after ingestion, the T waves in CF_5 have reverted to their control configuration.

in the height of the T waves, which become peaked with a narrow base.[18]   Thomson[9] found in a case of Addison's disease that when the serum potassium fell from 31.6 mg. per cent to 8.3 mg. per cent the T waves decreased from 7 mm. to 1.5 mm.   However, cases of Addison's disease may present a high serum potassium with a flat T wave.   Upright T waves may become inverted at a potassium level of 47 mg. per cent,[21] and as the potassium level rises a depression of the R-ST segments occurs.   Auriculoventricular block and intraventricular block may occur and there may be a disappearance of the P waves due to auricular

standstill.[1]   In the experimental animal, a level of 14.7 to 15.8 meq. will produce ventricular fibrillation and cardiac arrest.

There are numerous reports which would indicate that there may be no real correlation between the serum potassium concentration and the electrocardiographic changes.[18,21,34]   In familial periodic paralysis, during the episode of paralysis the serum potassium may be 50 per cent below normal* and the electrocardiogram show low, broad T waves with a disturbance in auriculoventricular conduction.   The administration of potassium salts will relieve the paralytic symptoms and improve the electrocardiogram without raising the serum potassium level.[16,20]   Disturbances in auriculoventricular and intraventricular conduction, and depression of the R-ST segments are common to both the hyper- and hypokalemic state.[26]

The serum potassium level is not an accurate guide to the intracellular potassium concentration.[18]   In many instances the potassium level does not rise after the administration of the salt.   This may be due to the fact that potassium distributes itself through a volume larger than that of the extracellular fluid and therefore must enter the body cells and be stored there temporarily.[18]

This report reveals also no parallelism between the potassium level and the alterations in the electrocardiogram (Table I).   Those patients who received the smaller dose of potassium salts (5 Gm.) with no significant rise in the serum potassium concentration developed pronounced electrocardiographic changes as did those patients who received the larger dose.   Conversely, patients who were given 15 Gm. of potassium salts with a subsequent rise in the serum potassium from 5.8 to 9.4 meq. demonstrated no important changes in the electrocardiogram.   This would indicate that the electrocardiographic changes do not depend entirely on the serum potassium level.

The upright trend of the inverted T waves occurred in Leads I, or CF$_5$, or both, for the most part.   In two cases only did Leads II and III show any significant alterations.   This must mean that the change in the repolarization does not uniformly affect the entire myocardium but is localized over the lateral portion of the left ventricle.

The normal trend of the inverted T waves through potassium therapy occurred within fifteen to sixty minutes in all cases but it was of a temporary nature.   The T waves were reinverted in all cases within two hours.†   However, in many instances the serum potassium was higher at this period.   This may mean that potassium is stored in the liver for some time or that complete absorption from the gastrointestinal tract may be delayed.

The normal contour of the inverted T waves produced by potassium salts is similar to that produced by ergotamine preparations in cases with a left ventricular preponderance.[37]   Scherf and Schlachman[37] were of the opinion that ergotamine preparations caused a change in the repolarization process by invoking a coronary vasoconstriction due to the direct action of these preparations

*In many instances there is no evidence of excess potassium excretion in the urine so that the low serum potassium must be due to a shift into the intracellular portion of the body tissue.[35]

†The temporary nature of the change is understandable, for it has been demonstrated at autopsy that potassium produces a functional rather than a structural alteration in the myocardium.[6]

on the coronary arteries.   Katz and Lindner[38] have shown experimentally that potassium produces a diminution in the coronary blood flow so that it is possible that potassium also causes a change in the repolarization process through its action on the coronary arteries.

Sharpey-Schaefer[23] proposed that potassium does not rise in the cells for many hours after ingestion and that the rapid electrocardiographic changes are caused, therefore, by the potassium changes in the extracellular fluid.   Potassium is known to play an important role in the membrane potentials of the myocardial fibers and will produce depolarization of the cell membranes in sufficient concentration or partial depolarization in lesser concentration.[39]

CONCLUSIONS

1.   Potassium salts are capable of causing an upright deflection of organically inverted T waves and therefore will not differentiate the organic from the functional T waves.

2.   There is no true correlation between the T-wave changes and the amount of potassium salt administered or the serum potassium level.

3.   The normalization of the inverted T waves is due to a change in the repolarization process which is rapid in onset as the upright deflection occurs within fifteen minutes and is of a temporary nature, for the waves revert to their original configuration within two hours.

4.   The mechanism by which the upright deflection occurs is uncertain, but the evidence seems to indicate a change in the membrane potentials of the myocardial fibers.

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QUINIDINE THERAPY OF AURICULAR FIBRILLATION

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IN THE past there has been considerable difference of opinion as to the indications and contraindications for quinidine. One contraindication that has been held by some is the occurrence of auricular flutter during the course of quinidine therapy of auricular fibrillation. White[4] states that ". . . if persistent auricular flutter appears, it is best to stop the quinidine. . ." It is our present purpose to show: (1) the frequency with which auricular flutter occurs in the course of quinidine therapy for the conversion of auricular fibrillation; (2) that the auricular flutter is not necessarily transitory, but may persist for days; (3) that continuation of quinidine therapy after auricular flutter develops will result in conversion to sinus rhythm in most instances; and (4) to analyze the factors of cardiac enlargement, congestive heart failure, and embolic phenomena in relation to quinidine therapy.

METHOD

To date forty-eight cases of auricular fibrillation have been carefully observed during the course of quinidine therapy. These consist of twenty-eight cases of arteriosclerotic heart disease, fifteen cases of rheumatic (mitral or mitral and aortic valvulitis) heart disease, four cases of thyrotoxicosis, and one undiagnosed heart lesion (possibly chronic "viral" myocarditis).

Group A includes twenty-six patients who developed auricular flutter during quinidine therapy with eventual conversion to a sinus rhythm. Group B includes eight patients who developed auricular flutter but could not be converted to a sinus rhythm. Group C includes fourteen patients who converted to a regular sinus rhythm without auricular flutter being demonstrated.

The duration of the fibrillation in most instances was unknown, but was believed to have been present for several months to several years. Digitalis was given to most patients prior to quinidine therapy. This was done to try to prevent the development of a 1:1 auricular flutter or a 2:1 auricular flutter with a rapid ventricular rate. In the few patients not given digitalis prior to the onset of quinidine therapy, digitalis was added during the course of quinidine administration.

All patients received oral quinidine. One patient in Group B also received quinidine "Enseals."* The usual initial dose (after drug sensitivity was tested)

was 0.2 Gm. every 2 hours for 5 doses daily, increasing the individual dose each day to 0.4 Gm., 0.6 Gm., and 0.8 Gm.

Electrocardiograms were taken at least once and usually twice daily. The auricular flutter may be missed clinically if a regular ventricular rate in the neighborhood of 80 is present since this could represent a 4:1 auricular flutter or even a 2:1 auricular flutter with a relatively slow auricular rate (160±) as the result of quinidine therapy. Leads II and V_1 were used routinely. In many instances V_1 was superior to II. It should be pointed out that "coarse" fibrillary waves (or flutter-fibrillation, impure flutter) are frequently seen in V_1 in auricular fibrillation. In this analysis great care was used to include as auricular flutter only those patterns which were unequivocal.

TABLE I. TOTAL CASES: 48

Group A.	Converted from auricular fibrillation →auricular flutter →regular sinus rhythm:	26 (54.2%)	70.9%
Group B.	Converted from auricular fibrillation →auricular flutter	8 (16.7%)	
Group C.	Converted from auricular fibrillation →regular sinus rhythm	14 (29.1%)	

TABLE II. ETIOLOGY OF HEART LESION

	*ARTERIOSCLEROTIC	RHEUMATIC	†THYROTOXIC	UNDIAGNOSED
Group A	16	6	4	
Group B	1	6		1
Group C	11	3		

*Includes group of hypertensive cardio-vascular disease and coronary artery disease.
†All patients were treated with propylthiouracil and Lugol's solution. The conversion was done at the time the patient was adequately treated and when the basal metabolic rate was zero or less.

TABLE III. DURATION OF AURICULAR FLUTTER

Group A: 1 to 7 days: average 1.9 days.

Group B: 1 to 6 days: average 3.4 days.

RESULTS

Of the forty-eight treated patients, thirty-four (Groups A and B) developed auricular flutter. Of these thirty-four, twenty-six (Group A) converted to a regular sinus rhythm when quinidine was maintained.

Eight patients (Group B) developed auricular flutter and were not converted to a sinus rhythm. Quinidine was purposely discontinued in two of these eight patients in whom flutter persisted for 48 hours. This was done early in the study and largely because of White's statement quoted heretofore. In one patient, sudden unexpected death occurred during the course of quinidine therapy on the fourth day of auricular flutter. It is believed that the death can in no way

be attributed to the auricular flutter, but was due to "cardiac and/or respiratory paralysis." The autopsy examination did not reveal any obvious cause of death. Two patients were given quinidine therapy in maximal amounts, one was given quinidine "Enseals" (with resulting high blood levels) in an attempt to reduce gastric distress, but without success. In these patients auricular flutter was maintained as long as quinidine was given, and when the drug was discontinued the rhythm reverted to auricular fibrillation. In the remaining three patients quinidine was discontinued because of the development of either numerous runs of ventricular ectopic beats or bundle branch block patterns. With discontinuance of quinidine the aberrant ventricular rhythm disappeared within 24 hours in all three patients, but in two the auricular flutter persisted for 48 hours after discontinuance of quinidine.

In Groups A and B, twenty-one patients developed a 2:1 auricular flutter during part of its duration. This occurred in spite of adequate digitalis therapy.

In Group C, fourteen patients (29.1 per cent) were converted from auricular fibrillation to a regular sinus rhythm without auricular flutter being detected as an intermediary event. In this group two patients developed nodal rhythm with auricular standstill. Regular sinus rhythm was established in both instances, in one with continuation of quinidine and in the other with stoppage of the quinidine when the nodal rhythm developed.

Cardiac enlargement, congestive heart failure and danger of embolic phenomena are frequently considered contraindications. For this reason the cases were analyzed accordingly (Table V).

Cardiac Enlargement: The degree of cardiac enlargement was based on actual size of the heart by roentgenograms in comparison with the predicted measurement. Up to 15 per cent over normal was considered mild enlargement, 15 per cent to 30 per cent moderate, and over 30 per cent marked enlargement. It can be seen in Table V that most of the patients had cardiac enlargement. It is true that the relative percentage of moderate and marked enlargement is greatest in Group B which failed to be converted. However, these are too few cases from which to draw a definite conclusion. In two patients the cardiac size decreased following conversion to sinus rhythm with simultaneous clearing of pre-existing congestive heart failure.

Congestive Failure: At one time this was considered a contraindication to administration of quinidine. However, at the present time most cardiologists feel the conversion of an auricular fibrillation to a regular sinus rhythm may considerably improve an otherwise resistant case of congestive failure. In Group A there were three patients who had persistent failure following the usual medical regime of rest, digitalis, salt-restriction, and diruetics. All three patients lost all signs of failure following conversion to a regular sinus rhythm.

Embolic Phenomena: This is undoubtedly the most feared complication of quinidine therapy. There is still considerable controversy as to whether conversion with quinidine does or does not increase the incidence of embolic phenomena. In this series ten patients had definite evidence of previous episodes of infarction, five systemic and five pulmonary. In none of these was there any

TABLE IV. EXAMPLES OF SEQUENCE OF EVENTS IN A FEW OF THE CASES IN GROUPS A AND B

CASE	SEX	AGE	DIAGNOSIS	DIGITALIS PRIOR TO QUINIDINE	VENTRICULAR RATE PRIOR TO QUINIDINE	QUINIDINE		
						DAY	DOSE	RESULT
1, Group A	M	62	Hyperthyroidism	Yes	80	1	0.2 gm. × 5	2:1 flutter with auricular rate = 190
						2	0.4 gm. × 5	4:1 flutter with auricular rate = 216
						3	0.4 gm. × 5	2:1 flutter with auricular rate = 190
						4	0.4 gm. × 5	2:1 flutter with auricular rate = 190
						5	0.6 gm. × 5	2:1 flutter with auricular rate = 240
						6	0.6 gm. × 5	4:1 flutter with auricular rate = 240
						7	0.6 gm. × 5	2:1 ⟷ 4:1 flutter with auricular rate = 190
						8	0.6 gm. × 5	2:1 ⟷ 3:1 flutter with auricular rate = 190
						9	0.6 gm. × 7	Regular sinus rhythm, rate = 65
						10	0.6 gm. × 3	
13, Group A	M	49	Rheumatic heart disease, mitral and aortic valvulitis	Yes	72	1	0.4 gm. × 5	2:1 ⟷ 4:1 flutter with auricular rate = 240
						2	0.6 gm. × 5	2:1 ⟷ 4:1 flutter with auricular rate = 240
						3	0.6 gm. × 5	2:1 ⟷ 4:1 flutter with auricular rate = 240
						4	0.8 gm. × 5	Regular sinus rhythm, rate = 68
						5	0.8 gm. × 7	
7, Group A	M	58	Arteriosclerotic heart disease	No / Yes	100	1	0.4 × 5	2:1 flutter with auricular rate = 300
						2	0.4 × 5	2:1 flutter with auricular rate = 300
						3	0.4 × 5 } plus full digitalization	2:1 flutter with auricular rate = 300
						4	0.6 × 5	2:1 ⟷ 4:1 flutter with auricular rate = 300
						5	0.6 × 5	Regular sinus rhythm, rate = 84
						6	0.8 × 5	

| 3, Group B | M | 51 | Rheumatic heart disease, mitral valvulitis | Yes | 76 | 1 0.4 gm. × 5   2:1 ⟷ 3:1 auricular flutter with auricular rate 250
2 0.6 gm. × 5   2:1 ⟷ 3:1 auricular flutter with auricular rate 215
3 0.8 gm. × 5   2:1 ⟷ 3:1 auricular flutter with auricular rate 215
4 0.8 gm. × 6   2:1 ⟷ 3:1 auricular flutter with auricular rate 215

Patient could not tolerate further quinidine because of nausea, vomiting, diarrhea, and tinnitus. Quinidine discontinued and auricular fibrillation recurred in 24 hours. Enteric coated quinidine sulphate was then used.

1 0.8 gm. × 5   2:1 ⟷ 3:1 auricular flutter with auricular rate 215
2 0.8 gm. × 5   2:1 ⟷ 3:1 auricular flutter with auricular rate 215
3 0.8 gm. × 8   2:1 ⟷ 3:1 auricular flutter with auricular rate 215
4 0.8 gm. × 5   2:1 ⟷ 3:1 auricular flutter with auricular rate 215

Quinidine was again discontinued because of severe diarrhea, vomiting, tinnitus, and prostration. Auricular fibrillation recurred in 24 hours. |
| 6, Group B | M | 52 | Rheumatic heart disease, mitral valvulitis | Yes | 74 | 1 0.4 gm. × 5   2:1 auricular flutter with auricular rate = 166;
2 0.6 gm. × 5
3 0.6 gm. × 5   all QRS complexes had the appearance of a right bundle branch block. Quinidine therefore discontinued.
4 None.   4:1 auricular flutter with auricular rate = 280, normal QRS complexes.
5 None.   4:1 auricular flutter with auricular rate = 320, normal QRS complexes.
6 None.   Auricular fibrillation |

TABLE V.   INCIDENCE OF CARDIAC ENLARGEMENT

CARDIAC ENLARGEMENT	GROUP A	GROUP B	GROUP C	TOTAL
None	6		3	9
Mild	12	3	6	21
Moderate	4	3	3	10
Marked	4	2	2	8
Congestive failure persisting prior to quinidine	3	3		6
Embolic phenomena prior to quinidine	5 {3 Systemic, 2 Pulmonary}	4 {1 Systemic, 3 Pulmonary}	1, Systemic	10
during or immediately after quinidine	0	0	2, Systemic	2

evidence of embolic phonomena during or after conversion to sinus rhythm. In Group C two patients suffered cerebro-vascular accidents during conversion which were probably embolic in origin. The first patient developed a nodal rhythm with auricular standstill for approximately 24 hours and then converted to a regular sinus rhythm at which time a right hemiplegia developed. It is possible that the period of auricular standstill contributed to the thrombus formation from which an embolus was thrown off when the auricles resumed regular contractions. The second patient was not observed in any other rhythm between auricular fibrillation and a regular sinus rhythm. He developed a sensory aphasia with no other neurological signs at the time of conversion. This cleared completely within one week. Neither of the above two patients had received anticoagulant therapy prior to quinidine. A few other cases have been treated with Dicumarol for approximately two weeks prior to quinidine therapy, the rationale being to prevent formation of fresh interauricular thrombi. However, there have been too few cases to be of statistical value.

DISCUSSION

Up to recent years the mechanism of auricular flutter has been generally accepted as the circulation of an excitation wave and contraction along a ring of muscle about the great veins in the right auricle. Sherf[2] suggested, from experimental work on dogs, that auricular flutter was the result of rapid stimulus formation in one center, and was not the result of a circus movement. Prinzmetal[5] conclusively proved this in his experimental studies, showing that auricular flutter was the result of a stimulus in one center and not a circus movement. Furthermore the occurrence of auricular flutter or auricular fibrillation was dependent upon the rate of the auricular stimulation. With an increasing rate the auricular flutter changed to auricular fibrillation. It is an established fact that quinidine slows the rate of auricular stimuli in auricular fibrillation. It is therefore logical to conclude that a slowing of auricular fibrillation will result in auricular flutter. Ramos and his co-workers[3] in their studies on auricular fibrillation artificially induced by acetylcholine, noted that the most frequent mode of termination of the fibrillation was transformation first into auricular flutter and then into a normal sinus rhythm.

Lewis[1] in 1922 showed that when quinidine was given to patients with auricular fibrillation an impure flutter usually developed, but that a pure flutter developed in only one case in ten. It was his opinion that considerably more quinidine could be given without affecting the auricular flutter. He also noted that auricular flutter did not occur simultaneously with the development of abnormal ventricular complexes. Both are at variance with our experiences as given heretofore.

After a few trial methods, our present method of quinidine administration is as follows: After a sensitivity test with 0.2 Gm., the patient is started on 0.2 Gm. every 2 hours for 5 doses. The individual daily dose is raised to 0.4 Gm. the second day and to 0.6 Gm. the third day. This latter dose is then maintained for three days. If auricular fibrillation or flutter still persist the dosage is increased to 0.8 Gm. Occasionally an extra dose is given at midnight to maintain a high blood level. It is essential that the attending physician should check with the patient prior to each increased dose of quinidine, questioning for symptoms of toxicity and carefully recording the heart rate, the rhythm, and the blood pressure. At present, quinidine blood levels are being determined at the times of appearance of auricular flutter and of conversion to a regular sinus rhythm. Too few of these have been done to date to warrant inclusion in this study.

Following conversion to normal rhythm the required maintenance dose varied considerably. In the average patient, 0.4 Gm. four times daily maintained a regular sinus rhythm.

SUMMARY

1. Auricular flutter is a common result of quinidine therapy given for conversion of auricular fibrillation to normal sinus rhythm.

2. The appearance of auricular flutter is in itself not a contraindication to continue quinidine therapy. In most instances if the dosage of quinidine is maintained or increased, conversion to a regular sinus rhythm will result.

3. Cardiac enlargement and congestive heart failure in themselves are not contraindications to quinidine therapy. The danger of embolic phenomena remains a possibility, but since this occurs even more commonly if the auricular fibrillation persists, it cannot be considered a definite contraindication.

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PRODUCTION OF RHEUMATIC SUBCUTANEOUS NODULES

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THE artificial production of subcutaneous nodules in rheumatic fever was first reported by Massell, Mote, and Jones, in 1937.[1] They postulated that trauma was important in the production of subcutaneous nodules. They were able to produce nodules artificially by taking 2 to 3 c.c. of whole blood from one arm of the patient and injecting it subcutaneously over the opposite olecranon. For the next ten days, the patients were instructed to apply frictional pressure to the injected elbow by rubbing it on the bedclothes several times a day. By this technique they were able to produce artificial nodules in two to three weeks which were clinically indistinguishable from naturally occurring nodules. In 90 per cent of twenty patients with clinical rheumatic fever, nodules developed. In patients with only laboratory evidence of rheumatic fever, 50 per cent of twenty-six patients developed nodules. In cases of inactive rheumatic fever, 14 per cent of fourteen patients developed nodules. Three per cent of the controls developed nodules. Novocaine was incapable of producing nodules whether friction was applied or not. It was considered by the authors that the size of the nodule produced and its duration were directly related to the activity and to the persistence of the disease.

Naturally occurring and artificially produced subcutaneous nodules were found to be very similar grossly and histologically. Many different descriptions of the histology of naturally occurring subcutaneous nodules appear in the literature. Mote, Massell, and Jones[2] believed that this was due to a difference in the age of the nodule. Biopsies of naturally occurring and artificially produced nodules under one month of age showed edema, fibrin deposition, and slight cellular infiltration. Nodules one to three months old revealed vascular damage with polymorphonuclear and lymphocytic infiltration, and proliferation of the primitive perivascular mesenchyme and other cells, which invaded the collagen foci. Nodules over three months' duration presented gradual organization, starting from perivascular areas toward the areas of necrosis with a cellular reaction of basophilic mononuclear and multinuclear cells arranged in a pallisade formation. There was progressive organization with fibrous tissue replacement. The difference between naturally occurring and artificially produced nodules was the presence of blood cells and phagocytes in the latter.

Hart, in 1939,[3] attempted to determine if the above results were due to trauma alone and/or to actual deposition into the tissues of a nodule-forming substance in rheumatic subjects. Using the technique of Massell, Mote, and Jones, ten

adults with rheumatoid arthritis, twenty children with acute and subacute rheumatic fever, twenty children with inactive rheumatic fever, and four patients with Still's disease were tested. In no case was a nodule produced. Blood from four patients with rheumatic fever who were forming nodules spontaneously was injected into patients with rheumatoid arthritis, active rheumatic fever, and Still's disease. The result was entirely negative. In two cases, patients developed nodules spontaneously in areas other than the injected site. This was felt to be coincidental.

Mirsky, in 1945,[4] postulated that nodule formation in rheumatic fever was due to the action of proteinases on mesenchymal tissue. These proteinases are released from tissue cells by trauma or an anaphylactoid reaction. Persons who develop rheumatic fever are those who are unable to inhibit these proteinases. With this thought as a basis, he injected a trypsin solution subcutaneously over the ulna of patients with rheumatic fever. Nodules were reported to have been induced, in 4 to 7 days, in 70 per cent of 145 patients convalescing from rheumatic fever. Thirteen per cent of the seventy-five controls were said to have developed nodules. No friction was used in any of the cases. A small group, number not stated, of patients with rheumatoid arthritis, Mirsky stated, reacted with nodules like the rheumatic fever group. No mention is made of histologic examination of any of the nodules.

Using the technique of Massell, Mote, and Jones and of Mirsky, we have attempted to produce nodules in patients with rheumatoid arthritis, rheumatic fever, and in normal subjects. All patients were adults, some were bed patients, others attended the out-patient clinic. They may be grouped as follows:

1. *Whole Blood Method.*—

a. Eighteen patients had rheumatoid arthritis. Twelve patients were female; six were male. All but three were in the active stages of the disease. One was classified as having Stage I (early) rheumatoid arthritis[5]; six were Stage II (moderately advanced); eleven were Stage III (far advanced). Two patients had naturally occurring nodules.

b. Eight patients had rheumatic fever. All of these were female. Seven were in the active stages of the disease. Three had arthritis without carditis; four had rheumatic carditis without arthritis; one had arthritis and carditis. None had naturally occurring nodules.

c. Five were normal subjects, without any rheumatic history or complaints. Three subjects were female; two were male.

2. *Trypsin Method.*—

a. Thirteen patients had rheumatoid arthritis. Eight were female, five male. All but three were in the active stages of the disease. Two were classified as having Stage I (early) rheumatoid arthritis; two were Stage II (moderately advanced); seven were Stage III (far advanced); and two were Stage IV (terminal). Five patients had naturally occurring nodules.

b. Six subjects had rheumatic fever. Five patients were female; one was male. Three were in the active stages of the disease. Two had arthritis and carditis; four had carditis without arthritis. None had naturally occurring nodules.

c.   Five were normal subjects without any rheumatic history or complaints. Two subjects were female; three were male.

3.   *Joint Fluid Method.—*

a.   Eight patients had rheumatoid arthritis. Six of these were female; two were male. Six were in the active stages of the disease. Five were Stage II (moderately advanced) rheumatoid arthritis; two were Stage III (far advanced); one was Stage IV (terminal). Two had naturally occurring nodules.

b.   Four patients had rheumatic fever. Three were female; one was male. Three were in the active stages of the disease. Three had arthritis and carditis; one had carditis without arthritis. None had naturally occurring nodules.

c.   Five were normal subjects without any rheumatic history or complaints. Three subjects were female; two were male.

METHODS

*Whole Blood Method.—*Three cubic centimeters of blood were taken from the antecubital vein of the right arm and injected subcutaneously over the left olecranon process.   This produced a sizeable bulge which was slightly painful for a few minutes.   The patients were instructed to rub the area vigorously with the other hand or on the bed sheets for ten minutes three times a day.   Before the injection of blood, the olecranon area was infiltrated subcutaneously with 3 c.c. of a 0.5 per cent procaine solution.

*Trypsin Method.—*One cubic centimeter of a Seitz-filtered, one per cent solution of crystalline trypsin magnesium sulfate compound, prepared according to the method of Kunitz and Northrop,[6] in M/400 hydrochloric acid, was injected subcutaneously over the left olecranon process.*   The solutions were used within forty-eight hours of their preparation.   No friction was applied to the injected area.   An attempt was made to use a 5 per cent solution of crude trypsin for injection, according to the method of Mirsky.[4]   It was not found possible to make such a solution.   Mirsky,[7] when referring to a 5 per cent solution, apparently meant a filtrate of such a mixture.   His study referred primarily to the use of crystalline trypsin magnesium sulfate compound, prepared according to the method of Kunitz and Northrop.[6]

*Joint Fluid Method.—*Fluid was obtained from the knee joint of a female patient who had Stage II (moderately advanced) active rheumatoid arthritis and naturally occurring subcutaneous nodules.   The fluid was bottled and tested for sterility through the courtesy and cooperation of the Department of Immunology, Department of Health, New York City.   After a preliminary sensitivity skin test, consisting of an intracutaneous injection of 0.1 c.c. of a 1-100 dilution of joint fluid, 1 c.c. of sterile joint fluid was injected subcutaneously over the olecranon process.   Friction was applied, as described above.

RESULTS

Whole Blood Method (after six weeks' observation).—(a) None of the patients with rheumatoid arthritis developed nodules.   (b)   One of the patients with

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*Raw material was obtained through the courtesy of Dr. M. Kunitz, Rockefeller Institute, Princeton, N. J.

rheumatic fever (active carditis without arthritis or naturally occurring nodules) developed what might clinically have been considered suggestive of a nodule. At the time of injection she developed the usual swelling which persisted for two weeks. The swelling did not have the appearance of a true rheumatic nodule. It did not have a definite contour but rather was an area of induration. Biopsy of this induration two weeks after injection revealed two ill-defined areas of granulation tissue in the fibro-adipose tissue, which was infiltrated by a few round cells and larger macrophages. No blood pigment was seen. No necrosis or fibrinoid changes were seen in the collagen (see Fig. 1).*   (c)   None of the control subjects developed nodules.
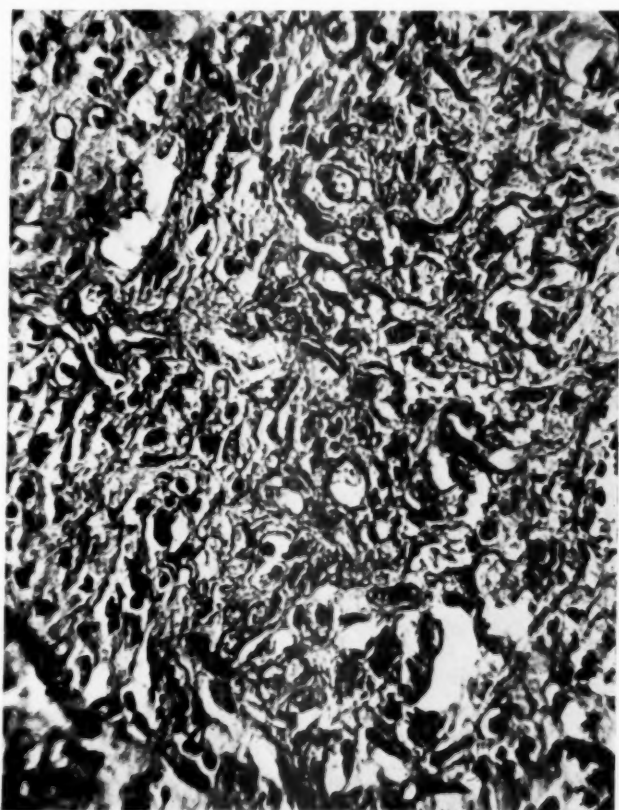

Fig. 1.—Biopsy of swelling produced by subcutaneous injection of whole blood demonstrates nonspecific granulation tissue.

Trypsin Method (after six weeks' observation).—None of the patients with (a) rheumatoid arthritis or (b) rheumatic fever developed nodules. None of the (c) control subjects developed nodules.

Joint Fluid Method (after six weeks' observation).—None of the patients with (a) rheumatoid arthritis or (b) rheumatic fever developed nodules. None of the (c) control subjects developed nodules.

*The biopsy was examined by Dr. H. Spitz, Department of Pathology, Bellevue Hospital.

DISCUSSION OF RESULTS

In the one patient who developed a persistent induration at the site of injection of blood, the pathological report was that of an inflammatory reaction and not that of an early rheumatic nodule formation. About one-half of the patients with rheumatoid arthritis were out-patients who were not under constant supervision but were seen only once a week. The patients with rheumatic fever and the control subjects were hospitalized patients and were under constant observation. Those injected with blood and joint fluid were closely watched to see that friction was applied to the injected site.

An attempt was made, in the selection of cases for injection, to use patients having varied stages of rheumatoid arthritis, to include active and inactive cases, and to inject those with and without naturally occurring nodules. In the rheumatic fever group, active and inactive cases were chosen. Some had arthritis or carditis, others had both. See Table I.

The results were negative in that nodules were not produced experimentally. In none of the patients used in this study was there any deleterious effect noted from the injection of whole blood, trypsin, or joint fluid. In no instance was there any change in the clinical status of the rheumatic disease or any alteration in the erythrocyte sedimentation rate. No electrocardiographic changes occurred.

SUMMARY

The production of rheumatic subcutaneous nodules was attempted in thirty-nine patients with rheumatoid arthritis, in eighteen patients with rheumatic fever, and in fifteen normal controls (1) by the injection of whole blood over the olecranon, applying friction to the injected area; (2) by injecting a solution of trypsin over the olecranon; and (3) by injecting joint fluid from a patient with active rheumatoid arthritis over the olecranon and applying friction. Patients in various stages of the disease, active and inactive, with and without naturally occurring nodules, were used. No nodules were produced experimentally in any case.

TABLE I.   RESULTS OF INJECTION OF WHOLE BLOOD, TRYPSIN, AND JOINT
FLUID INTO NORMAL CONTROLS AND RHEUMATIC PATIENTS

	SUBSTANCE USED		
	WHOLE BLOOD	TRYPSIN	JOINT FLUID
Rheumatoid Arthritis—			
Active	15	10	6
Inactive	3	3	2
Rheumatic Fever—			
Active	7	3	3
Inactive	1	3	1
Normal Controls	5	5	5

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SUBACUTE BACTERIAL ENDOCARDITIS OF NONSTREPTOCOCCIC ETIOLOGY

A Review of the Literature of the Thirteen-Year Period 1936-1948 Inclusive

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THE viridans or alpha-hemolytic streptococcus is the causative organism in 90 to 95 per cent of cases of subacute bacterial endocarditis; the remaining cases are due to a wide variety of other microorganisms, of which many are unusual and interesting. Most of the organisms are ordinarily considered as feebly pathogenic, but, when present in sufficient numbers in a susceptible host, may give rise to this infection.

Such a diversity of organisms as *Corynebacterium diphtheriae, Escherichia coli, Brucella abortus, Diplococcus pneumoniae, and Hemophilus influenzae* have been reported occasionally in endocarditis cases in the past thirteen years. With the advent of sulfonamide and antibiotic therapeutic measures, it is more important than ever before to isolate and identify the etiological agents, in order that adequate treatment may be carried out.

This review of the literature and presentation of bibliography of the thirteen-year period, 1936-1948, includes all microorganisms other than streptococci which have been reported as etiological agents of the disease. All streptococci, whether designated as viridans, hemolytic, nonhemolytic, enterococcus, Streptococcus s. b. e., etc., have been excluded. Duration of illness of five to six weeks has been taken as the lower limit. Therapeutic measures have not been included, although the period of observation on apparently-recovered patients has been noted. Tabulation has been made here only of the causative organism, numbers of cases reported, previous cardiac history, heart lesions of cases coming to autopsy, and recoveries. Foreign literature which has been difficult to obtain has been read only when the title gave indication of the causative organism; a few articles have been included by title only.

Two hundred and twelve cases of endocarditis have been presented in detail, 115 have been mentioned only in the literature, and 22 titles are included. In the detailed group there were 46 apparent recoveries after various treatment procedures, with observation periods varying from a few days to several years. Autopsies were carried out on 144 of the 166 fatal cases; the mitral valve was the

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site of vegetations **48** times, the aortic **41**, the pulmonary **12**, and the tricuspid **10**; combinations of mitral and aortic lesions occurred in **22** cases, mitral and pulmonary in **2**, mitral and tricuspid in **2**, and aortic and tricuspid in **2**; three valves (mitral, pulmonary, and tricuspid) contained lesions in one instance. The chordae tendinae were involved twice, the wall of the right auricle once, and definite endocarditis without mention of the affected valve three times.   Rheumatic heart disease had been present in **50** of the **212** cases; **12** presented congenital lesions, and **9** had previous syphilitic heart damage; there were **3** cases of scarlet fever and **3** of chorea; rheumatic heart disease plus a congenital lesion, and syphilis plus a congenital lesion occurred once each, as did rheumatic heart disease plus chorea, mitral stenosis, and hypertensive heart disease.   In the others either mention was not made of previous cardiac disease, or detailed histories did not reveal evidence of previous rheumatic involvement.

A complete list of the microorganisms involved follows (terminology corresponds to Bergey's Manual of Determinative Bacteriology, ed. 6, Baltimore, 1948, The Williams and Wilkins Company.

Pseudomonas aeruginosa
Micrococcus aureus, M. albus, M. citreus
Neisseria gonorrhoeae, N. meningitidis (intracellularis), N. catarrhalis, N. flava, N. pharyngis, N. perflava
Brucella abortus, B. melitensis, B. suis, B. bronchiseptica
Hemophilus influenzae, H. parainfluenzae, H. aprophilus
Diplococcus pneumoniae, many types
Paracolon bacillus
Escherichia coli
Salmonella schottmülleri, S. choleraesuis, S. typhosa, S. typhimurium
Klebsiella pneumoniae
Corynebacterium diphtheriae, C. haemolyticum, C. diphtheriticum
Mycobacterium tuberculosis
Actinomyces bovis, A. graminis, A. septicus
Treponema
Spirillum minus
Streptobacillus moniliformis (Haverhillia)
Lactobacillus
Actinobacillus lignieresi
Clostridium perfringens (welchii)
Erysipelothrix rhusiopathiae
Nocardia
Histoplasma capsulatum
Candida (Monilia) albicans, C. parakrusei, C. guillermondi
Diplococcus crassus
Grahamella
Veillonella gazogenes
Pasteurella tularensis
Dialister

BRIEF TABULATION OF CASES

ORGANISM AND REFERENCE	CASE HISTORIES DETAILED	CASE HISTORIES MENTIONED	TITLES	CARDIAC HISTORY		HEART PATHOLOGY		APPARENT RECOVERIES
Pseudomonas aeruginosa: 89, 95, 131	3			Mital stenosis	1	Mitral Aortic Mitral and aortic	1 1 1	
Micrococcus: 5, 6, 31, 47, 48, 49, 50, 52, 54, 65, 74, 78, 93, 103, 105, 115, 116, 118, 119, 124, 125, 129, 137, 139, 142, 144, 147, 173, 174, 182, 188, 194	29	18		Rheumatic heart disease Congenital lesion Syphilis Chorea	11 4 1 1	Mitral Mitral and aortic Aortic	4 4 6	12 Observations 3 months to 4 years
Neisseria gonorrhoeae: 13, 21, 27, 28, 39, 45, 51, 62, 63, 70, 71, 72, 80, 87, 99, 100, 109, 128, 134, 135, 138, 143, 145, 159, 162, 164, 167, 170, 178, 196, 197, 204	42	39	2	Rheumatic heart disease Congenital lesion Rheumatic heart disease plus congenital lesion Scarlet fever	3 1 1 1	Aortic Mitral Pulmonary Tricuspid Mitral and pulmonary Mitral and tricuspid Mitral and aortic Unmentioned	11 8 5 4 1 1 2 1	7 Observation 1 month to 1 year
Neisseria meningitidis (intracellularis): 7, 10, 42, 55, 56, 81, 99, 136a, 193, 198, 203	15			Rheumatic heart disease Rheumatic heart disease plus chorea Scarlet fever	1 1 1	Mitral Mitral and aortic	4 1	7 Observation 10 days to 4 months
Other Neisseria: 36, 37, 43, 77, 121, 166a, 169, 191	10	2		Rheumatic heart disease	3	Mitral Aortic Tricuspid, pulmonary, and mitral	2 1 1	4 Observation 2 months to 4 years
Brucella: 29, 34, 46, 53, 93, 98, 108, 139, 149, 151, 152, 154, 170, 171, 175, 176, 177, 189	15		3	Rheumatic heart disease Congenital lesion Syphilis	7 1 1	Mitral Aortic Mitral and pulmonary Mitral and aortic	4 6 1 1	2 Observation 3 weeks to 6 months
Hemophilus: 16, 19, 24, 38, 88, 92, 96, 106, 107, 110, 114b, 126, 130, 136b, 139, 140, 147, 156, 158, 166b, 168, 194, 201	17	6	2	Rheumatic heart disease Congenital lesion Syphilis Scarlet fever Chorea	5 1 1 1 1	Mitral Aortic Pulmonic Tricuspid Mitral and aortic	4 1 1 1 2	6 Observation at least 10 months

Organism (reference numbers)				Associated heart disease	Valve / site involvement	Observation
Diplococcus pneumoniae: 4a, 11, 20, 25, 30, 32, 40, 57, 65, 68, 79, 84, 86, 92, 94, 101, 104, 112, 113, 150, 160, 172, 183, 184, 202	19	45	2	Rheumatic heart disease 2 Congenital lesion 2 Hypertensive heart disease 1 Syphilis 1	Mitral 2 Mitral and aortic 2 Mitral and tricuspid 1 Tricuspid 5 Pulmonary 2 Tricuspid and aortic 1 Endocardium 1	Observation 1 to 5 months 3
Gram-negative rods of enteric group: 4b, 22, 35, 58, 59, 65, 67, 75, 127, 133b, 140, 153, 157, 179, 181, 192, 199b	15	1	3	Rheumatic heart disease 5 Congenital lesion 1	Mitral 8 Aortic 4 Pulmonary 1 Aortic and tricuspid 1 Wall right auricle 1	
Corynebacterium: 64, 76, 90, 102, 136b, 148, 180, 187	3		5	Rheumatic heart disease 1	Mitral 1 Aortic 1	
Mycobacterium tuberculosis: 9, 14, 15, 44, 73, 82, 122, 165	8		1	Rheumatic heart disease 2	Mitral 2 Mitral and aortic 1 Pulmonary 2 Chordae tendinae of tricuspid 1	
Actinomyces: 1, 2, 12, 60, 116, 117, 185, 190	6	1	2	Rheumatic heart disease 1	Mitral 2 Aortic 1 Mitral and aortic 1	Observation 16 months 1
Treponema: 66, 155, 186	3			Syphilis 2 Congenital lesion plus syphilis 1	Aortic 2 Mitral 1	
Miscellaneous organisms, *Spirillum, Lactobacillus, Actinobacillus Clostridium, Erysipelothrix, Nocardia, Histoplasma, Candida, Haverhilia, Veillonella, Pasteurella, Dialister,* others: 3, 8, 12, 17, 18, 26, 33, 41, 61, 69, 83, 85, 88, 89, 91, 97, 111, 114a, 120, 123, 132, 133, 141, 146, 147, 161, 163, 195, 199a, 200	27	3	2	Rheumatic heart disease 9 Congenital lesion 2 Syphilis 3 Chorea 1	Mitral 5 Mitral plus aortic 6 Aortic 7 Pulmonary 1	Observation 9 months to 2 years 4

168, 194, 201   Chorea 1   Mitral and aortic 2

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ARTERIOSCLEROTIC AORTIC INSUFFICIENCY

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A ORTIC insufficiency in elderly patients with hypertension and arterio-sclerosis is not an unusual condition. This report comprises seventeen patients 59 to 75 years of age observed in private practice during the past few years. In most of these patients the aortic diastolic murmur appeared while under personal observation.

There are many references in the literature to hypertensive, degenerative, or arteriosclerotic aortic insufficiency. Osler[1] and Vaquez[2] recognized its occurrence in patients with hypertension and chronic nephritis. In 1930, Gager[3] mentioned three patients with aortic insufficiency of arteriosclerotic origin. The first patient had uremia with dilatation of the aorta and thickening of the aortic valves; the second had a dissecting aortic aneurysm; and the third had hypertension. He observed that the aortic regurgitation in a hypertensive individual was not necessarily syphilitic in origin, but might be due to atheromatosis or dilatation of the aorta. In such patients he found the aortic second sound to be often accentuated and immediately followed by the diastolic murmur of aortic regurgitation.

A series of 200 consecutive cases of chronic hypertension was studied at necropsy and reported by Garvin[4] in 1940. In fourteen of this group the murmur of aortic insufficiency had been detected during life. Since the post-mortem findings in these fourteen cases revealed normal aortic valves with dilatation of the aortic ring in only some, he termed them cases of "functional aortic insufficiency." In only two patients was there evidence of syphilitic aortitis, both without involvement of the aortic valves.

Gouley and Anderson[5] in 1940, studied six patients with systolic and diastolic aortic murmurs, which at autopsy were found to be due to chronic dissecting aortic aneurysms. The murmurs were interpreted as being caused by the distortion and relaxation of the aortic ring resulting from the dissection.

In 1942 Peery[6] reported eleven hypertensive patients developing aortic insufficiency in which the post-mortem examinations disclosed intimal tears of the aorta, usually just above one or more commissures. In many the intimal tear did not go on to an actual dissection of the aorta, but the subsequent scar tissue did produce a weakening of the involved commissure with ptosis of the attached semilunar valves thus leading to their incompetence. He stated that an incomplete intimal tear was probably more common than a dissecting aneurysm. Peery mentioned that the clinical diagnosis might be surmised in a hypertensive patient with a negative Wassermann reaction who developed aortic systolic and diastolic murmurs after an attack of pain in the chest with dyspnea.

Table I.

CASE	PATIENT SEX	AGE	OBSERVATION PERIOD	CLINICAL DIAGNOSIS*	DURATION OF HYPERTENSION	DEGREE OF CARDIAC FAILURE†	OCULI FUND†	BLOOD PRESSURE BEFORE AORTIC INSUFFICIENCY	BLOOD PRESSURE AFTER AORTIC INSUFFICIENCY	AORTIC DIASTOLIC MURMUR AND DURATION	AORTIC SECOND SOUND‡	AORTIC SYSTOLIC MURMUR†	AORTIC DILATATION†	LEFT VENTRICLE ENLARGEMENT†	STATUS
1	C. T. male	71	3	Xanthoma tuberosa; angina	6	III	II	170/90	103/60	Loud 2 months	<	IV	II	I	Died myocardial infarction, 1947
2	P. L. female	68	17	Osteoarthritis; angina	6	0	II	175/90	210/90	Short 3 years	>	III	II	II	Moderate activity
3	J. K. male	75	13	Osteoarthritis; angina	25	0	II	200/110	190/70	Short 3 months	N	II	II	III	Moderate activity
4	I. W. female	59	15	Angina; osteoarthritis	20	I	III	220/140	240/120	Loud 1 year	>	III	III	III	Moderate activity
5	S. A. male	65	6	Vascular disease of legs; angina	12	II	II	220/110	180/90	Short, faint 2 months	>	III	II	IV	Sudden death, 1946
6	H. C. male	70	11	Heart block; angina	25	II	III	180/90	240/70	Short, faint 4 months	>	I	II	II	Moderate activity
7	S. H. male	64	11	Osteoarthritis; angina	20	III	II	170/80	200/70	Loud squeaking 2 years	>	III	III	III	Died heart failure, 1949
8	J. U. male	72	8	Prostatism; angina	10	0	II	210/110	210/90	Long 1 year	>	III	III	III	Moderate activity
9	C. B. female	72	10	Osteoarthritis	10	I	II	195/100	195/95	Short, loud 3 years	>	II	III	II	Moderate activity
10	J. M. male	64	8	Bronchiectasis	4	IV	II	165/90	185/80	Short	N	II	III	IV	Died heart failure, 1948
11	R. R. female	66	4	Diabetes, angina	10	0	III	210/110	230/80	Faint, high-pitched 1 year	>	III	II	I	Moderate activity
12	A. M. female	72	12	Secondary anemia	10	0	II	150/90	170/70	Long, loud 5 years	N	I	I	0	Moderate activity
13	L. D. male	63	1	Diabetes; uremia	10	II	III		240/120	Rough, squeaking	>	II	II	III	Died in uremia, 1949
14	L. R. female	74	1	Hyperthyroidism	?	0	II		200/80	Short, faint	>	II	II	I	Moderate activity
15	S. S. female	67	2	Angina	10	0	II		220/80	Long, loud	N	I	III	II	Moderate activity
16	I. S. male	67	11	Diabetes; osteoarthritis; angina	11	II	III		170/60	Long, loud	N	II	III	IV	Limited activity
17	P. H. female	60	10	Angina	15	0	II	210/110	220/80	Short, faint 1 year	>	III	II	II	Moderate activity

*The clinical diagnosis omits hypertension and arteriosclerosis, present in all the patients, and congestive heart failure which is listed under the degree of cardiac failure.
†Gradiations are 0 to IV where 0 is normal and IV is the maximum.
‡ > indicates the aortic second sound is increased. N indicates normal, and < indicates decreased.

Gouley and Sickel[7] in 1943 observed eleven patients with aortic regurgitation and varied periods of hypertension, in which post-mortem examination revealed dilatation of the aortic orifice. In some, a saccular dilatation of the ascending aorta was also found. The semilunar leaflets were observed to be stretched and incompetent as a result of dilatation of the aortic ring. The subsequent mechanical regurgitation often produced an erosion, followed by thickening in the mid-portion of the free edge of all three aortic leaflets with the disappearance of the normal corpora aurantii, while the lateral margins of the leaflets remained intact. In some cases the commissural junctions were widened into actual furrows from stretching of the aortic ring, and the semilunar valve attachments were thereby loosened, increasing the degree of the insufficiency. Microscopic sections showed fibrosis and sclerosis limited to the free margins of the middle part of the aortic valves without increased vascularity or focal cellular infiltration such as occurs in rheumatic infections. They commented that these gross valvular lesions of mechanical regurgitation might easily be missed unless especially looked for.

Gouley and Sickel[7] noted that their patients were about 60 years of age, had no serologic evidence of syphilis and no clinical evidence of subacute bacterial endocarditis. The murmur of aortic insufficiency had rather limited transmission and often merged with an accentuated aortic second sound. The pulse pressure was moderately increased with an elevated systolic pressure up to 200 mm. Hg and a lowered diastolic pressure below 100 mm., but never below 50 mm. Hg. The pulse was mildly Corrigan in type, but there were neither capillary pulsations, Duroziez's murmur nor Traube's pistol-shot femoral sound.

Hamman[8] in 1944 described relative aortic insufficiency occurring with aortic dilatation in the late stages of prolonged hypertension. In these cases the semilunar valves did not approximate. Peripheral circulatory manifestations were usually absent and the aortic diastolic murmur frequently varied in intensity at different times. Actual arteriosclerosis of the semilunar valves producing the insufficiency was rather rare, although he observed one case where the attachment of two semilunar valves was involved by atherosclerosis. Hamman also noted the frequency of aortic insufficiency coexisting with calcific aortic stenosis.

PRESENTATION OF CASES

The seventeen patients summarized in Table I were observed in my office and do not include several others seen on hospital rounds. In thirteen of the patients the aortic diastolic murmur initially appeared while under my care and then persisted. All were aware of hypertension for periods of from 4 to 25 years, the average being 11.5 years. Eight patients were female and nine were male, all being white. Their ages varied from 59 to 75 years with an average of 67 years. They were under treatment from 1 to 18 years, the average period of direct observation being 8 years.

All patients revealed evidence of arteriosclerosis in the peripheral arteries and the fundi oculi. The fundi showed at least grade II changes, and in five hemorrhages and exudate were also seen. In all seventeen, the serologic tests were reported negative for syphilis. No patient gave a suggestive history of any

rheumatic infection. Angina pectoris was present in twelve of the patients, in most both before and after the appearance of the aortic regurgitation. Nine suffered from slight to severe congestive heart failure. Five had myocardial infarctions at some time, and in almost all the electrocardiograms showed various degrees of myocardial damage. Three of the patients also had diabetes mellitus, one had hyperthyroidism, one had bronchiectasis, and one had diffuse xanthoma tuberosa.

In the entire series, before the appearance of diastolic murmur the systolic blood pressure ranged from 150 to 220 mm. Hg with a mean of 193 mm. Hg. The diastolic blood pressure varied from 80 to 140 mm. Hg with an average of 98 mm. Hg. After the appearance of the murmur, the average systolic pressure rose to 206 mm. Hg, while the average diastolic pressure fell to 85 mm. Hg. In almost all the pulse pressure increased with the onset of the aortic regurgitation, the carotid pulsations appeared somewhat more prominent, and the pulse became moderately Corrigan in type. However, there were no other peripheral arterial findings of aortic insufficiency in any of the patients. It should be noted that some patients had a relatively low diastolic pressure even before the appearance of the murmur which was probably secondary to a loss of elasticity in the aorta. The patient in Case 2 is interesting in that she has been observed for 17 years, the first 11 years being without hypertension with a blood pressure of about 130/80 mm. Hg. Hypertension of 175/90 mm. Hg then developed, and after three years the diastolic murmur appeared, the average blood pressure then becoming 210/90 mm. Hg.

The aortic second sound was accentuated in eleven patients, and in two it exhibited a tambour quality. In five others the aortic second sound was of normal intensity, while in the remaining patient the sound was diminished. In general, it was observed that the intensity of the second sound did not change after the advent of the insufficiency.

All seventeen patients revealed an aortic systolic murmur, usually harsh, varying from grade I to grade IV (grade IV regarded as maximal), the average being grade III. One patient (Case 1) had a palpable aortic systolic thrill and was later found to have also calcific aortic stenosis. The systolic murmur was interpreted as being due to dilatation, tortuosity, and intimal atherosclerotic roughening of the aorta.

The aortic diastolic murmur observed in all the patients was usually heard best at Erb's area in the third interspace to the left of the sternum, although sometimes it was more apparent directly over the aortic area. In some it was transmitted downward as far as the cardiac apex. It was often of short duration and seemed to be fused with and to follow the accentuated aortic second sound. However, it was in all cases a distinct diminuendo diastolic murmur of a definite duration and was not to be confused with the reverberation so frequently heard after a loud second sound. The murmur was of great intensity in nine patients but was rather faint in the other eight, so that it was at times difficult to distinguish following the louder aortic systolic murmur which seemed to fatigue the ear. In some it was necessary to concentrate on the diastolic period only, with observer and patient not breathing, in order to detect the murmur. In

several patients the murmur could be heard clearly at one visit and not at the next, only to reappear at a subsequent examination.

On fluoroscopic or teleoroentgenographic examination, the left ventricle was found to be enlarged in all the patients and varied from grade I to grade IV enlargement (where grade IV is regarded as the maximum). The average left ventricular enlargement was grade II, although eight patients had marked expansion of the left ventricular chamber, especially those with heart failure. The ascending aorta and aortic arch were dilated in all the patients, the average being grade II (where grade IV is considered the maximum). In six patients, the aorta was markedly dilated and suggested a beginning aneurysm.

Of this series of seventeen patients, congestive heart failure occurred in nine; it was of moderate nature in six and in three of such severity as to cause death. Another patient died of cerebral thrombosis and uremia, while one died suddenly in his store and an autopsy was not performed. One other patient is quite disabled and partly bedridden. The remaining eleven are still ambulatory and active, being able to perform light work.

CASE REPORTS

CASE 1.—C. T., a man aged 71 years, was first treated in 1944. He had had hypertension for three years and frequent attacks of angina pectoris for the previous fifteen years, and was dependent upon nitroglycerin for relief. He also had suffered from severe joint pains for the past twenty years. Hard subcutaneous nodules had appeared on the dorsum of his hands and fingers, elbows, knees, Achilles' tendons, and the right big toe. A biopsy of one nodule had shown xanthoma tuberosa. The blood cholesterol content had been reported as 500 mg. per cent. One sister, one brother, and three sons were similarly affected. At his first examination the heart revealed rough apical and aortic systolic murmurs, the left ventricle was slightly enlarged, and the aorta was moderately dilated. The blood pressure was 170/90 mm. Hg.

In June, 1947, two months before the patient's demise, a loud aortic diastolic murmur became audible for the first time over the precordial area with maximum intensity at the left sternal border. The apical systolic murmur remained as formerly, but the aortic systolic murmur became louder and rougher and was accompanied by a palpable thrill. The aortic second sound diminished in intensity while the pulmonic second sound became accentuated. With the advent of the aortic insufficiency, the congestive failure became worse. A severe attack of chest and epigastric pain required his readmission to the hospital where death occurred on the fifth day, in August, 1947.

Necropsy revealed a recent posterior wall infarction and congestive changes as the immediate cause of death. The aortic cusps were firm and sclerotic, standing away from the wall of the aorta, which also was markedly sclerotic and moderately dilated. The coronary ostia and arteries were intensely sclerotic and partially occluded by atheromatous plaques. There was a complete occlusion of the right coronary artery 1 cm. from its origin. Microscopic sections of the aortic cusps showed calcification and extensive fibrosis. The left lung revealed considerable fibrosis.

The aortic pathology was interpreted as calcific aortic stenosis and insufficiency of arteriosclerotic origin.

CASE 2.—P. L., a woman aged 68 years, has been under care since 1932 for symptoms referable to osteoarthritis and paroxysmal tachycardia. Her blood pressure ranged about 130/80 mm. Hg until 1943, when it gradually rose to 175/90 mm. Hg. In 1945 exertional precordial pain appeared, which was relieved by rest and nitroglycerin, and the electrocardiogram then revealed left axis deviation with left ventricular strain. In 1946, a short, puffing, aortic diastolic murmur was first heard, particularly over the aortic area, and this murmur has persisted until the present.

The aortic diastolic murmur is now best heard over Erb's area with the patient holding her breath in deep expiration. A loud apical systolic murmur and a harsh aortic systolic murmur are also present. Her most recent blood pressure reading was 210/90 mm. Hg.

CASE 3.—Mr. J. K., aged 75, has been under my care for hypertension and generalized osteoarthritis since 1936. During this period he has experienced precordial pain on exertion with relief by rest. On the initial visit his blood pressure was 165/90 mm. Hg and the left ventricle showed moderate enlargement. In the subsequent eleven years the patient has manifested a progressive rise in his blood pressure to 200/110 mm. Hg. A rough aortic systolic murmur has become audible, while the aorta became moderately dilated and the left ventricle considerably enlarged.

In August, 1949, a short, distinct, aortic diastolic murmur was heard over the left sternal area and has persisted to the present. His last recorded blood pressure was 190/70 mm. Hg. The patient is still able to engage in light activities. Fig. 1 is a recent teleoroentgenogram of his chest.
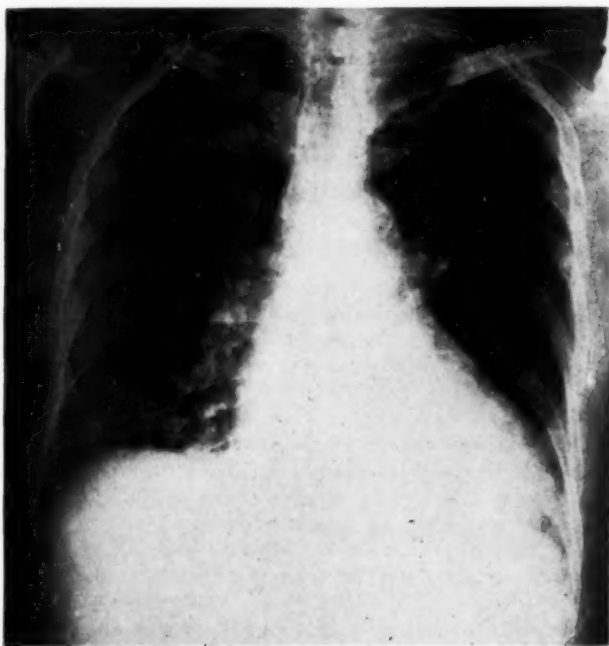
Fig. 1.—J. K., Case 3. Teleoroentgenogram taken in September, 1949. There is considerable (grade III) enlargement of the left ventricle and moderate (grade II) dilatation of the aorta. A calcified plaque is evident in the aortic arch.

CASE 4.—I. W., a woman aged 59 years, has been observed since 1934. On her first visit she presented a history of known hypertension since 1929. Examination at that time revealed a blood pressure of 178/110 mm. Hg, grade II fundi, slight left ventricular prominence, and slight aortic dilatation. The patient continued to feel well despite a gradual rise of her blood pressure to 220/140 mm. Hg until 1942, when she began to suffer from attacks of angina pectoris. Progressive dilatation of the aortic arch and enlargement of the left ventricle became apparent. This is shown in Fig. 2.

In 1948, a loud aortic diastolic murmur immediately following a sharply accentuated aortic second sound first became evident. The murmur was heard best over the left sternal border and was transmitted downward almost as far as the cardiac apex. A loud, rough systolic aortic murmur and a moderate systolic apical murmur were also present. With the appearance of the aortic insufficiency, the patient developed slight congestive heart failure responding to treatment. Her most recent blood pressure was 240/120 mm. Hg. She is still performing light household duties and is ambulatory.

DISCUSSION

In this group of seventeen elderly patients, aortic insufficiency became evident after an average of over ten years of persistent hypertension.   The term "functional aortic insufficiency," as mentioned by Garvin,[4] seems inadequate since the regurgitation, once developed, became permanent.   The term aterio-sclerotic aortic insufficiency is therefore preferred because the condition is found
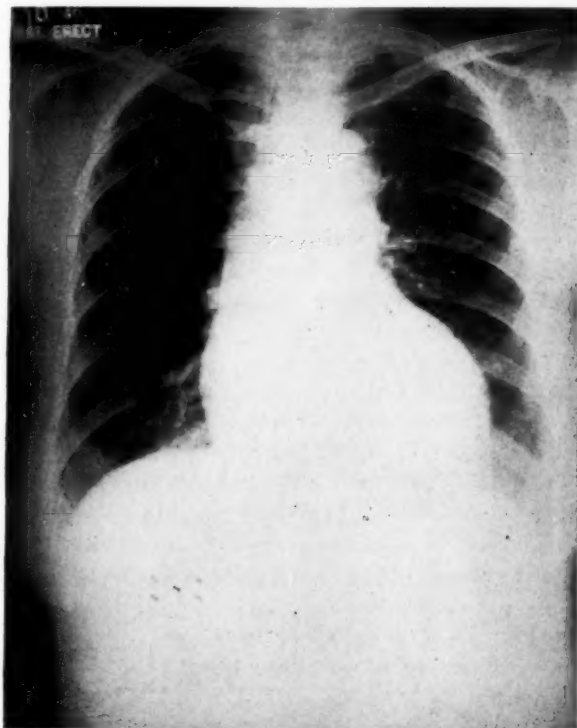

Fig. 2.—I. W., Case 4.   Teleoroentgenogram taken in October, 1946.   There is considerable (grade III) enlargement of the left ventricle and marked (grade III) dilatation of the aorta.

principally in patients with extensive arteriosclerotic involvement of the ascending aorta, which is usually dilated, as well as in other branches of the arterial system.   It is possible that some of these patients might have had rheumatic infections without any history.   However, in thirteen of the seventeen patients the aortic diastolic murmur appeared while under direct observation.

The degenerative changes leading to aortic insufficiency described in the literature are also best included under the general terminology of arteriosclerotic involvement of the root of the aorta.

Only one of my patients, Case 1, was examined at necropsy, and he revealed calcification of the aortic semilunar valves leading to both stenosis and insufficiency, the process being secondary to extensive atherosclerosis of the aorta and

its valves. It is probable that a similar lesion, which produces the harsh aortic systolic as well as the diastolic murmur, may be present in other patients of this series. This has been noted by Hamman.[8]

The group of seventeen patients presented in this paper indicates that arteriosclerotic aortic insufficiency is by no means a rare condition in the older aged group with prolonged hypertension. Regurgitation should be carefully looked for in any such individual with a high pulse pressure, high systolic and relatively low diastolic pressure, although loss of normal elasticity of the aorta alone may account for such pressure variations. The examiner should listen over the left sternal and the aortic area while the patient is holding his breath in expiration, and should concentrate on the diastolic phase of the heartbeat immediately after the accentuated aortic second sound. The murmur of regurgitation should have a definite duration and should not be confused with the reverberation common after an accentuated second sound. One may hear the murmur at one visit and not at the next, but this is not unusual with all aortic diastolic murmurs. In these patients the peripheral manifestations of the aortic insufficiency are only moderate, the pulse being somewhat Corrigan in type and the carotid pulsations appearing slightly more prominent than in the uncomplicated hypertensive patient.

SUMMARY

Arteriosclerotic aortic insufficiency was diagnosed in a series of seventeen patients averaging 67 years of age, with a history of prolonged hypertension. In thirteen the aortic diastolic murmur first appeared while under personal observation.

In most instances the advent of the insufficiency had little adverse influence on the prognosis.

Aortic insufficiency of arteriosclerotic origin is by no means a rare condition and should be looked for in elderly individuals with chronic hypertension exhibiting a high pulse pressure.

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ISOLATED INTERVENTRICULAR SEPTAL DEFECT WITH DILATATION OF THE PULMONARY ARTERY

Including a Discussion of the Mechanism of Pulmonary Vascular Sclerosis in Congenital Heart Disease

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THE occurrence of dilatation of the pulmonary artery in association with isolated interventricular septal defect is most unusual. The clinical significance of this entity lies in the radiologic differential diagnosis from patent ductus arteriosus, interatrial septal defect, Eisenmenger's complex, idiopathic dilatation of the pulmonary artery, and pulmonic stenosis with post-stenotic dilatation. The post-mortem finding of pulmonary arteriosclerosis in addition to the dilatation of the pulmonary artery throws some light on the pathogenesis of these lesions.

In 1879, Roger[1] described congenital isolated interventricular septal defect, a congenital anomaly not associated with cyanosis. The lack of symptoms, the mesocardial, harsh, holosystolic murmur, the minimal cardiac enlargement, and the good prognosis were the characteristic features of this condition. By post-mortem studies Abbott[2] confirmed the fact that there was little change in the relative size of the ventricles and none in the size of the pulmonary artery and aorta. Brown[3] considered the loud, harsh, systolic murmur, maximal at the third and fourth left intercostal spaces close to the sternum, as pathognomonic. The roentgenogram of the heart was usually normal. Globular enlargement, though mentioned, was considered infrequent. Enlargement of the pulmonary artery and its branches was considered to be exceptional and was attributed to an associated lesion. A normal electrocardiogram or left axis deviation was obtained most frequently. Taussig's[4] description of the findings in ventricular septal defect was identical. Dr. Taussig included in her discussion the very high septal defects at the base of the aorta involving the aortic septum and resembling the defect in the frank Eisenmenger lesion. Dilatation of the pulmonary artery did occur in these cases, but not in the usual case of Roger's disease. Welch and Kinney[5] found no dilatation of the pulmonary artery in eleven cases examined postmortem. In a review of the literature Selzer[21] found reports of dilatation of the pulmonary artery in the presence of large interventricular defects.

Our clinical experience confirms the rarity of dilatation of the pulmonary artery in association with isolated ventricular septal defect. Moreover, where angiocardiography was done in thirty selected cases of typical isolated inter-

ventricular septal defect in children and adults, the pulmonary artery and branches were found to be of normal size.

MATERIAL

1. J. R., 4 months old, and A. D., 6 months old, were encountered during the clinical examination of 250 patients with congenital heart disease during the past two years.

2. H. M., 3 years old, died suddenly after tonsillectomy.

3. The clinical observations and post-mortem findings of these three patients are presented herewith.

CASE HISTORIES

CASE 1.—H. M., a white female child 3 years of age with a history of congenital heart disease and mental retardation, was admitted twenty-four hours after tonsillectomy with fever of 108° F. Bleeding during the operation was minimal. Codeine had been administered rectally for postoperative restlessness. The physical examination was curtailed because of the marked prostration, shock, extreme dyspnea, tachypnea, and cyanosis. There was no evidence of obstruction of the airway. Despite emergency treatment, the patient died within two hours after admission to the hospital.

Post-mortem Findings: (1) Interventricular septal defect with hypertrophy and dilatation of the right and left ventricles. (2) Dilated and thickened pulmonary artery tree, involving the peripheral pulmonary branches as far distally as the subpleural parenchyma. Microscopic examination of the large pulmonary vessels revealed thickening of the media and the intima. There was also intimal proliferation with narrowing of the lumina of the smaller arteries. (3) Pulmonary atherosclerosis. (4) Pulmonary congestion, atelectasis, and emphysema. (5) Acute bronchitis with early bronchopneumonia. (6) Severe fatty change of the liver and kidneys.

Comment.—This 3-year-old white child was not seen by us at any time before the last two hours of her life. It is known, however, from the referring physician that the child was not cyanotic. Nothing is known about the location or quality of the murmur. The electrocardiographic findings are not available. Significantly, an interventricular septal defect is present in association with a dilated pulmonary artery, the circumference of which (4.0 cm.) is slightly greater than the normal aorta (3.5 cm.). The maximal thickness of the left ventricular muscle (1.2 cm.) is greater than that of the right ventricle (1.0 cm.). The atria are normal. The thickening and dilatation of the main pulmonary artery are also characteristic of the entire pulmonary tree, including the small arteries. In addition, there is intimal proliferation of the smaller arteries with narrowing of the lumen. These anatomical changes represent the effects of the congenital defect over a period of three years. The anatomical changes in the pulmonary arteries and particularly the intimal proliferation in the smaller branches could be interpreted as being associated with ante-mortem pulmonary hypertension. Whether such hypertension was actually present is unknown.

The ventricular defect itself is high and is situated just below the posterior and right aortic cusps. The shunt through the defect is, however, directed a little downward and across into the right ventricle at the septal cusp of the tricuspid valve. The blood stream has hollowed out a portion of the anterior wall of the right ventricle, where the endocardium is fibrosed (Fig. 1,*A* and *B*).
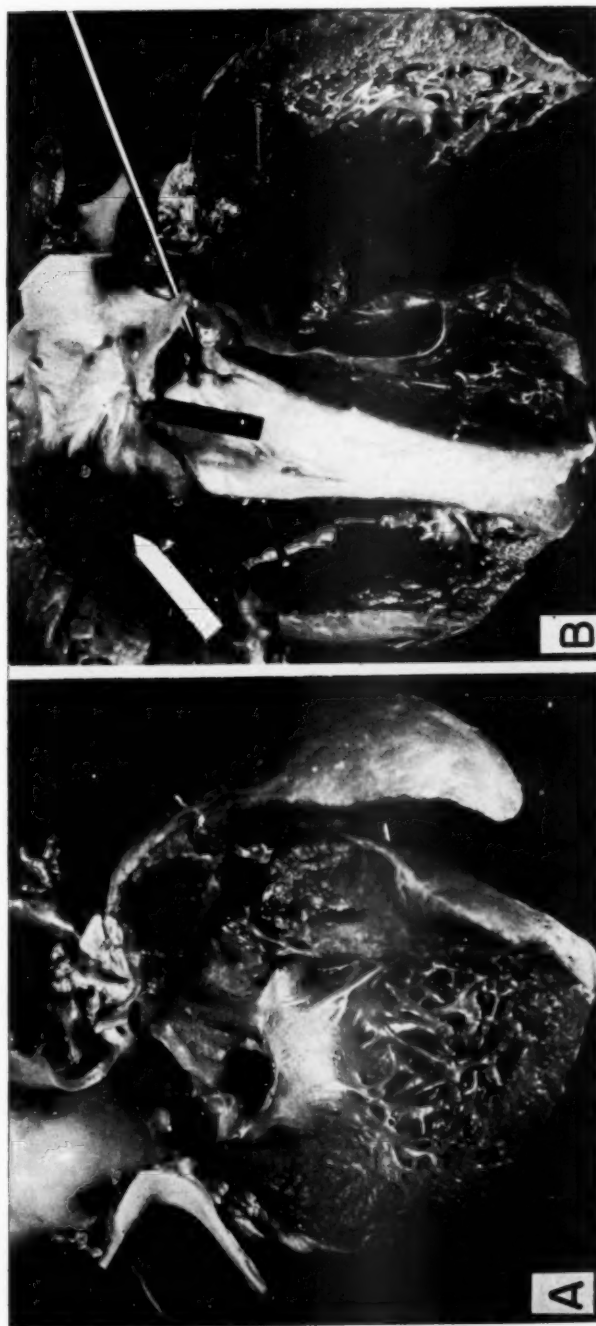
Fig. 1.—H. M. *A*, Interventricular septal defect and hypertrophied left ventricle. *B*, White arrow indicates hollowed-out portion of anterior wall of right ventricle. Black arrow indicates dilated pulmonary artery. Probe is through septal defect.

The cause of death is obscure, but in all likelihood the high fever and the acute pulmonary infection increased the cardiac burden due to the interventricular defect and resulted in heart failure.

CASE 2.—A. D., a white male infant 6 months of age, was admitted with a history of three episodes of cyanosis, three weeks before, two days before, and on the day of admission, respectively. The cyanosis was related to exertion, either crying or straining; on two occasions it was necessary to employ artificial respiration.

The child was born after a normal labor and delivery. When the patient was 3 months of age, a diagnosis of congenital heart disease was made at another hospital. The lesions considered were interatrial and interventricular septal defects. At that time a radiologic density was noted in the left lower lung field and was interpreted as an area of atelectasis or pneumonitis. Nine days later a similar density was noted in the left upper lung field.

Because of the diagnosis of atelectasis, repeated bronchoscopic drainings were done two months before admission. Some secretion was aspirated from the left main bronchus. Smear and culture were not helpful in establishing a diagnosis. Following the bronchoscopies, the left upper lobe was said to have been re-aerated. The density in the left lower lobe, however, persisted. The patient was admitted to this hospital because of labored respiration, cough, and one attack of cyanosis.

Physical Examination: The patient was a 6-month-old white male infant, pale, poorly developed, and poorly nourished, weighing 12 pounds, 8 ounces. There was tachypnea with an expiratory grunt. There was a grayish pallor of the skin, but no cyanosis. An occasional unproductive cough was present. The ears, nose, and throat were normal. The trachea was in the midline. The chest was emphysematous in contour and there was a precordial bulge. The lungs were resonant throughout. However, there were high-pitched musical râles in both lung fields anteriorly and posteriorly, many more in the right and left upper lobes. The heart was enlarged to the right and to the left. There were no thrills. There was a loud, harsh, low-pitched systolic murmur maximal at the third left intercostal space, transmitted along the left sternal border to the apex but not toward the base. There was no diastolic murmur. The rate was 200 per minute. The rhythm was regular. The liver and the spleen were slightly enlarged.

Laboratory Examination: The hemoglobin was 8.3 Gm. per 100 c.c. of blood. There were 3.27 million red blood cells per cubic millimeter. There were 5,950 white blood cells per cubic millimeter of blood with 7 per cent nonsegmented forms, 27 per cent segmented forms, 63 per cent lymphocytes, 2 per cent monocytes, and 1 per cent basophiles. The urine was normal.

X-Ray Examination: "The thoracic cage is widened. In the P-A view, there is marked cardiac enlargement to the left. The heart shadow fills most of the left lung field. The apex is rounded and extends to the lateral border of the thoracic cage. The pulmonary artery segment is very prominent and is continuous with the rounded apex. The prominent bulging pulmonary artery is well demonstrated in the right oblique view."

Electrocardiogram: "Sinus tachycardia, rate 187 per minute. No axis deviation. S_1, S_2, and S_3 are small. P_1 is bifid. There is a tall R with high voltage and a small S in CR_1 and CR_2. An equiphasic QRS is recorded at CR_5. The standard leads are not remarkable. The pattern in the precordial leads may indicate right ventricular hypertrophy."

Course: At the time of admission the temperature was 99° F. By the second hospital day, despite the use of penicillin and oxygen, dyspnea and cough increased. Although the respirations were difficult and noisy, with marked pulling and substernal retraction, there was no cyanosis. The temperature reached 104° F., where it remained until death on the morning of the third hospital day.

Post-mortem Findings: (1) Interventricular septal defect with dilatation and hypertrophy of the right and left ventricles. (2) Dilatation and thickening of the pulmonary artery and its peripheral branches. Microscopically, the intrapulmonary branches showed thickening of the adventitia and media but no intimal proliferation or encroachment on the lumen. (3) Pulmonary congestion and atelectasis of the left lower lobe.

Comment.—This 6-month-old infant had experienced respiratory symptoms at the age of 3 months. A diagnosis of pulmonary atelectasis or pneumonitis was made at this time. The course until death was characterized by intermittent cyanosis associated with atelectasis which necessitated bronchoscopy for aspiration of bronchial secretion. During the last hospital admission, atelectasis, pulmonary infection, and respiratory difficulty again characterized the clinical picture. It was felt that the entire illness could be explained on the basis of pressure of a markedly enlarged heart on the mediastinal structures and on the left lung. Death was thought to be due to heart failure secondary to the pulmonary process and the associated anoxia.

The nature of the cardiac lesion was diagnosed before death by the location and quality of the murmur and by x-ray findings. The loud, harsh, low-pitched systolic murmur maximal in intensity at the left third intercostal space and decreasing in intensity at the base was characteristic of interventricular septal defect. The electrocardiographic findings in the precordial leads of right ventricular hypertrophy and the presence of a prominent pulmonary artery were disquieting features, because these findings are usual in interatrial septal defect.

These discrepancies were clarified by the post-mortem examination, which showed the presence of an interventricular septal defect in association with a dilated, thickened pulmonary arterial tree. In this case there was no encroachment on the lumen of the smaller intrapulmonary arteries by intimal proliferation. The aorta was small (2.5 cm.) and the main pulmonary artery was dilated (4.0 cm.).

The septal defect was situated just below the right aortic cusp and the direction of the shunt was directly across into the right ventricle in the region of the septal cusp of the tricuspid valve (Fig. 2,*A* and *B*).

CASE 3.—J. R., a white female infant 4 months of age, was admitted because of diarrhea of eighteen days' duration and failure to gain weight. Gestation and delivery were normal. Cyanosis, present at birth, had disappeared completely. Ten weeks before admission, pharyngitis and cough were successfully treated with steam inhalation. Six days before admission, acute bilateral otitis media responded to penicillin therapy. Periods of tachypnea and dyspnea had been noted intermittently since birth.

Physical Examination: The infant was well developed but relatively small and pale. Cyanosis and clubbing were absent. Tachypnea and slight dyspnea were present. There was exudate in the left external auditory meatus. The lungs were normal to auscultation and percussion. Cardiac dullness was increased to the left. A systolic thrill was felt at the third and fourth intercostal spaces to the left of the sternum. There were no thrills in the neck. A harsh, low-pitched, holosystolic murmur was heard maximally at the third and fourth intercostal spaces to the left of the sternum, its intensity decreasing at the aortic and pulmonic areas. The liver was just palpable.

Laboratory Examination: The hemoglobin was 11.5 Gm. per 100 c.c. of blood. The white blood cell count was 5,650 per cubic millimeter of blood, with 38 per cent polymorphonuclears, 10 per cent nonsegmented forms, 48 per cent lymphocytes, 2 per cent monocytes, and 2 per cent basophiles. The plasma carbon dioxide content and chloride level were normal.

X-Ray Examination: (Fig. 3). "The heart is enlarged to the right and left. The pulmonary artery segment is prominent. The hilar and peripheral vascular markings are prominent."

Electrocardiogram: (Fig. 4.) "Sinus tachycardia, rate 150 per minute. No axis deviation. Small S_1, Q_2, and Q_3 are present. P_2 is tall. T_1 is low. RS-T_1 and RS-T_2 are slightly depressed. The extremity leads show slight RS-T depression in aV_F and slight elevation in aV_R. The

Fig. 2.—A. D. A. Dilated pulmonary artery and enlarged right ventricle. B, Large interventricular septal defect.

precordial leads over the right midaxillary line and the right midclavicular line at the level of the fourth intercostal space do not indicate the presence of right ventricular enlargement.   The QRS complexes at positions V_1 to V_7 are normal for a child of this age.   The T-wave inversion in V_6 and V_7, the low T_1 and the RS-T depressions in Leads I and II probably indicate myocardial involvement secondary to tachycardia and toxemia.   Digitalis, however, is also a factor.   There is no evidence for a diagnosis of ventricular hypertrophy."

Phonocardiogram: (Fig. 5.) "The phonocardiogram clearly shows the murmur to be of highest amplitude at the third and fourth intercostal spaces to the left of the sternum.   The murmur at the base and at the apex is of much lower amplitude.   This conforms to the characteristics of the typical murmur of interventricular septal defect."
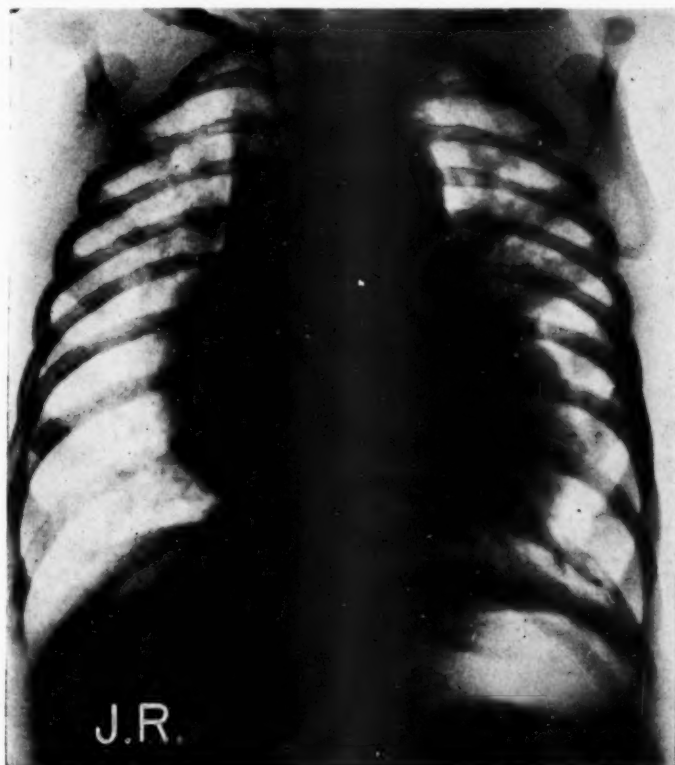
Fig. 3.—J. R., showing globular enlargement of the heart and marked prominence of the pulmonary artery and secondary branches.

Course: On the day after admission the temperature rose to 104.2° F.   Dyspnea, grunting expiration, tachypnea, and slight cyanosis characterized the clinical picture.   The eardrums were slightly reddened and there was consolidation in the right upper lobe.   The liver had become markedly enlarged.   The diagnosis of pneumonia and heart failure was considered.   Penicillin and sulfadiazine were administered.   The patient was digitalized in three doses (40 mg. of Digifolin per kilogram) and then maintained on 15 mg. of Digifolin orally.   There was marked improvement.   The liver became normal in size and in two weeks the lung signs cleared.   However, severe diarrhea began abruptly on the fourteenth hospital day.   Within twenty-four hours the temperature rose to 105° F. and the infant died from pulmonary edema.

Post-mortem Findings: (1)   Interventricular septal defect with hypertrophy and dilatation of the right and left ventricles.   (2)   Dilated and thickened pulmonary artery tree, involving the peripheral pulmonary branches as far distally as the subpleural parenchyma.   Microscopically,
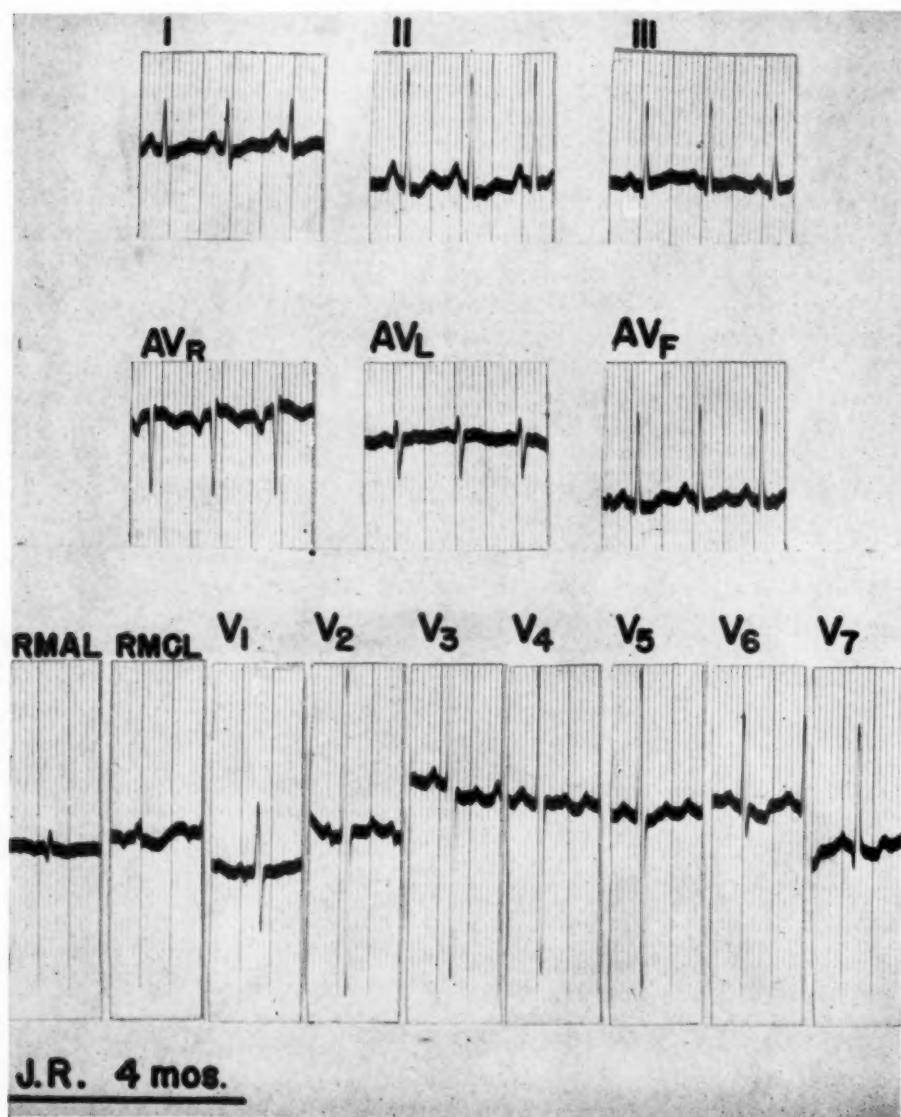
Fig. 4.—J. R. There is no evidence of chamber enlargement. RS-T and T wave changes in Leads I, II, aV$_F$, and V$_6$ and V$_7$ are secondary to tachycardia, toxemia, and digitalis.

there was thickening of the media and the intima of the main pulmonary artery. The media and adventitia of the smaller arteries were thickened, but there was no intimal proliferation or narrowing of the lumen. (3) Pulmonary congestion and minimal pulmonary edema. (4) Atelectasis of the right upper and right middle lobes of the lung.

Comment.—This 4-month-old infant had been ill since the age of 2 months. She was subject to respiratory infection, diarrhea, and in all likelihood to heart failure. The illness in the hospital was diagnosed as pneumonia and heart failure, and the infant responded to antibiotics and digitalis. Death was caused by heart

failure secondary to the toxemia of an acute fulminating diarrhea with a temperature of 105° F.

A diagnosis of interventricular septal defect associated with dilatation of the pulmonary artery was made before death on the basis of the characteristic murmur at the third and fourth intercostal spaces to the left of the sternum,
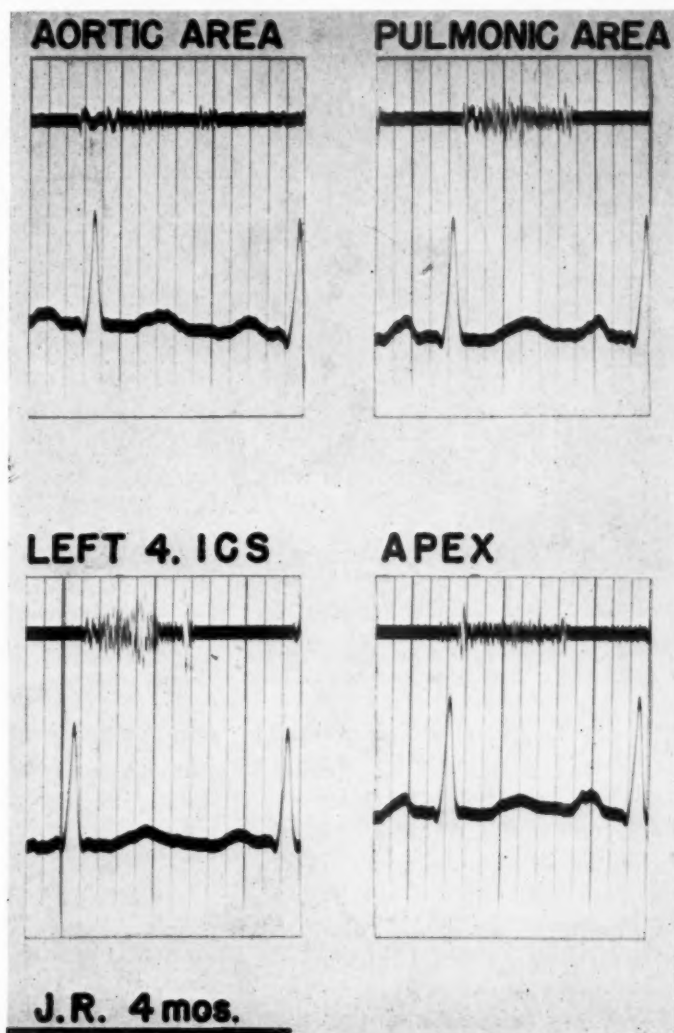
Fig. 5.—Crescendo systolic murmur of high amplitude is shown over the fourth intercostal space to the left of the sternum. The second pulmonic sound is accentuated.

the normal electrocardiogram, and the x-ray configuration of the heart. Postmortem examination confirmed the diagnosis. The pulmonary artery was dilated (3.5 cm.) and the aorta was small (2.0 cm.). In this case, as in Case 2, there was no encroachment on the lumen of the smaller, intrapulmonary arteries by intimal proliferation. The hypertrophy of both ventricles probably accounted for the absence of axis deviation and the normal standard leads.

The interventricular septal defect was situated more anteriorly at the base of the right aortic cusp. The shunt was directed diagonally to the right ventricle and slightly upward, so that there was endocardial thickening just below the pulmonic valve, the cusps of which were normal (Fig. 6).
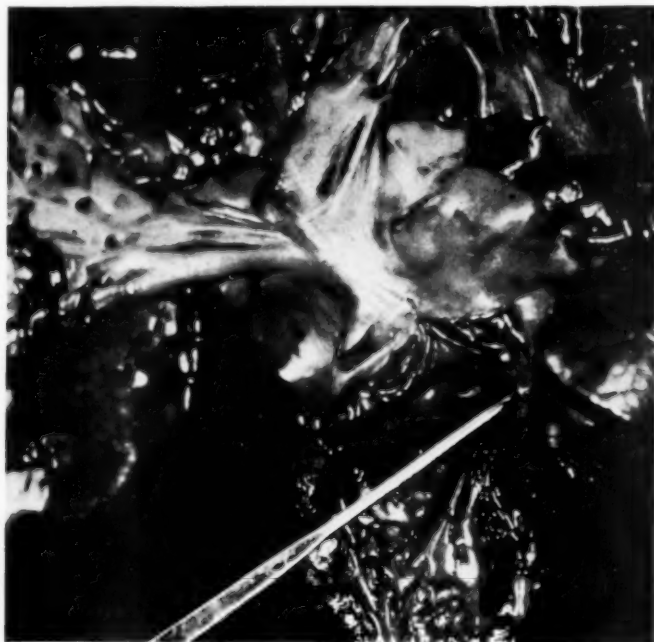

Fig. 6.—J. R.   Marked dilatation of the pulmonary artery and branches can be seen, extending to the periphery.   The probe is in the interventricular septal defect.

DISCUSSION

Anatomical Features.—(Table I) Isolated interventricular septal defect associated with a dilated pulmonary artery tree is an entity. The septal defect was relatively large in our cases. There was hypertrophy and dilatation of the right and left ventricles secondary to the shunt. The main pulmonary artery and all its branches, including the intrapulmonary, were dilated and thickened. The aorta was hypoplastic in the two infants and normal in the 3-year-old child. The intrapulmonary arteries showed dilatation with an increase in the thickness of the media and adventitia in all three cases. The smallest arteries showed no intimal proliferation in the two infants. However, there was intimal proliferation and narrowing of the smallest arteries in the 3-year-old child, whose main pulmonary artery showed gross atherosclerosis.

Pathogenesis of the Pulmonary Artery Dilatation.—The dilatation of the main pulmonary artery can conceivably be explained by a large ventricular septal defect, so situated high in the septum that a shunt of ventricular blood under high pressure balloons out the pulmonary artery.[4] In our cases there is no anatomical evidence for such an explanation. On the contrary, a ballooning and hollowing of the anterior wall of the right ventricle with endocardial fibrosis is

TABLE I.   ANATOMICAL FINDINGS

	H. M., AGED 3 YEARS	A. D., AGED 6 MONTHS	J. R., AGED 4 MONTHS
Right atrium	No dilatation. Slight hypertrophy.	Slight dilatation. Slight hypertrophy.	Slight dilatation. No hypertrophy.
Right ventricle	Marked dilatation. Marked hypertrophy (1.0 cm.).	Moderate dilatation. Moderate hypertrophy (0.5 cm.).	Slight dilatation. Moderate hypertrophy (0.8 cm.).
Pulmonary artery	Thickened. Dilated (4.0 cm.). Some yellow flecking.	Thickened. Dilated (4.0 cm.). No atherosclerosis.	Thickened. Dilated (3.5 cm.). No atherosclerosis.
Intrapulmonary arteries	Thickened. Dilated to periphery: intimal proliferation with narrowing.	Thickened. Dilated to periphery: no intimal proliferation.	Thickened. Dilated to periphery: no intimal proliferation.
Left atrium	No dilatation. No hypertrophy.	Slight dilatation. Slight hypertrophy.	No dilatation. No hypertrophy.
Left ventricle	Moderate dilatation. Moderate hypertrophy (1.2 cm.).	Moderate dilatation. Slight hypertrophy (0.8 cm.).	Slight dilatation. Moderate hypertrophy (1.2 cm.).
Aorta	Normal (3.5 cm.).	Small (2.5 cm.).	Small (2.0 cm.).
Interventricular defect	High (1.1 cm.).	High (1.5 cm.).	High (0.7 cm.)
Foramen ovale	Closed.	Closed.	Closed.
Ductus arteriosus	Closed.	Closed.	Closed.
Cardiac enlargement	Marked.	Marked.	Moderate.

present in Case 1, and represents the effect of the left to right shunt over a period of three years.   Furthermore, it is unlikely that the dilatation of the most peripheral pulmonary vessels is also caused by these hemodynamic changes.

Pulmonary hypertension secondary to the shunt must be considered a factor, particularly in the presence of arteriosclerotic changes in the pulmonary vascular tree.   If intimal sclerosis and narrowing were considered an indication of severe hypertension, one would have to conclude that severe pulmonary hypertension was not a dominant factor in two of our three cases.   This aspect of the pulmonary changes will be clarified later when the pathogenesis of the pulmonary vascular sclerosis is discussed.

From our studies, the most likely explanation for the dilatation of the entire pulmonary artery tree is that it is a primary congenital anomaly and not secondary to hemodynamic or pressure changes.   The presence of hypoplasia of the aorta and dilatation of the pulmonary artery in our two infants supports this hypothesis. Hypoplasia of the aorta and dilatation of the pulmonary artery are also seen in infants with interatrial defects who die at birth.   In these cases, a hemodynamic explanation is difficult, since the shunt during fetal life is from right to left atrium and not left to right.   Furthermore, dilatation of the pulmonary artery tree has

recently been noted in three mongoloid infants, $5\frac{1}{2}$ weeks, $2\frac{1}{2}$ months, and 6 months of age, each of whom had a common atrioventricular canal. The two youngest had no pulmonary vascular sclerosis. The oldest at 6 months of age had minimal changes. The presence of diffuse pulmonary artery dilatation soon after birth ($5\frac{1}{2}$ weeks) without pulmonary vascular sclerosis is again in favor of its developmental origin.

Pathogenesis of the Pulmonary Vascular Sclerosis.—Parker and Weiss[7] have suggested that a combination of three factors is necessary for the production of an abnormal degree of pulmonary arterial and arteriolar sclerosis: (1) high intravascular pressure, (2) stagnation of blood, and (3) pericapillary edema. In the presence of a left to right shunt, a fourth factor, increase in volume flow, may be in part responsible for the pulmonary vascular sclerosis.[5] Time is also a factor, although lesions can develop within one to two months.[7,8] It should be remembered also that changes in the smaller arteries, arterioles, and capillaries in turn increase the intravascular pressure which intensifies the vascular changes.

According to Parker and Weiss,[7] a combination of factors is necessary for the production of lesions. Sclerosis was absent in their control group of cases of pulmonary emphysema and congenital heart disease with hypertrophied right ventricle, where presumably pulmonary hypertension existed. The same conclusion can be reached from the studies of Welch and Kinney.[5] Pulmonary sclerosis in excess of that expected in controls of similar age was unusual in cases of left to right shunts, which included patent ductus arteriosus, interatrial defect, and interventricular defect. When mitral stenosis, congestive heart failure, or an additional congenital defect was associated with the left to right shunt, the incidence of sclerotic changes increased. The size of the shunt and hence the increase in pulmonary blood flow seemed to be a common factor but not the sole factor in the production of vascular lesions. Similarly, in one of our cases of tricuspid atresia with transposition of the great vessels[9] where a dilated pulmonary artery arose from the left ventricle, there was dilatation of the pulmonary artery but no changes in the peripheral pulmonary vessels despite the influence of left ventricular pressures.

The vascular lesions in the 3-year-old child include changes in the large arteries and intimal proliferation with narrowing in the smaller vessels. The changes in the two infants do not include intimal proliferation of the smaller arteries. The common factor in these cases is a large defect with an increase in the pulmonary blood flow. The presence of pulmonary hypertension can only be surmised to have been present in the 3-year-old child. Its presence in the infants is highly conjectural because of the lack of anatomical changes. If the dilatation of the pulmonary artery tree is congenital, as seems probable, these congenitally dilated vessels may be prone to medial and adventitial hypertrophy secondary to the increased blood flow and possibly to an increase in tension. Atelectasis, emphysema, and pneumonitis certainly are factors which must also be considered in the pathogenesis of the pulmonary sclerosis.

Physiological Considerations.—Since dilatation of the pulmonary artery associated with isolated ventricular septal defect is rare, the recent literature[5,10-21] was reviewed in order to ascertain whether such an association had been en-

countered. An analysis was made of the possible interrelationship of increased pulmonary blood flow, pulmonary hypertension, dilatation of the pulmonary artery, and pulmonary vascular sclerosis.

Many of the cases reported in the literature as interventricular defects cannot be accepted as isolated lesions.[10,14,16] The diagnosis in these cases is usually based on the oxygen difference between right atrial and right ventricular blood. However, in many instances the clinical findings, murmurs, electrocardiogram, and roentgen configuration suggest the presence of additional lesions. Nevertheless, the patients reported by Dexter[13] and Burchell and associates,[20] and the two patients reported by Cournand and associates[21] may be instances of isolated interventricular septal defects with a dilated pulmonary artery. Dexter's and Burchell's patients were 10 years and 12 years old, respectively. Both had elevated systolic and diastolic pressures in the right ventricle and pulmonary artery and high pressures in the right atrium in the absence of clinical heart failure. Electrocardiographically, right axis deviation was present in both cases, and a right ventricular hypertrophy pattern in one case. Cournand's first patient was 3 years of age and showed mild pulmonary and right ventricular hypertension. Again the diastolic end pressure in the right ventricle and the mean pressure in the right atrium were elevated despite the absence of clinical congestive failure. Cournand's second patient was 12 years old and also showed right ventricular and pulmonary hypertension. Thus, all four patients reported in the literature had pulmonary hypertension, a dilated pulmonary artery, and an interventricular septal defect. In one the pulmonary hypertension was very mild, suggesting that the pulmonary artery dilatation was independent of the pulmonary artery pressure.

The relationship of pulmonary hypertension to pulmonary artery dilatation remains a problem because of the lack of anatomical correlation. Moreover, there seems to be no constant relation between the size of a defect, the calculated pulmonary flow, and the presence of pulmonary hypertension. Patients with patent ductus arteriosus or interventricular septal defects may have no pulmonary hypertension despite a large defect and a large calculated pulmonary blood flow. Patients with interatrial defects (presumably some with dilated pulmonary arteries) may have a marked increased in blood flow and no pulmonary hypertension. That the pulmonary vascular bed can compensate for an increase in blood flow without resultant hypertension is well known. Welch and Kinney[5] cite a case which illustrates this lack of correlation. An interatrial defect measuring 2.5 cm. was present in a 57-year-old man who had been in mild congestive failure for one year. The pressure in the pulmonary artery was 35/10 mm. Hg (minimal systolic elevation) and the pulmonary blood flow was 14 liters per minute (markedly increased). Despite this very mild pulmonary hypertension, the pulmonary artery was dilated to 11 cm. in circumference and atherosclerosis was present. The peripheral pulmonary vascular lesions did not exceed those usually found in the sixth decade of life. One would be led to conclude in this case that the dilatation of the pulmonary artery was unrelated to the height of the pulmonary vascular pressure, and that the peripheral lesions were unrelated to the increase in the pulmonary blood flow.

Thus there is evidence that dilatation of the pulmonary artery may be congenital, and that the effect of pulmonary hypertension may be secondary. It is quite definite that an increased blood flow through a shunt need not lead to pulmonary hypertension. The relation of increased pulmonary blood flow to pulmonary artery dilatation and to pulmonary vascular sclerosis remains to be elucidated.

Clinical Considerations: The ordinary patient with isolated interventricular septal defect does not show pulmonary artery dilatation. The heart is not remarkably enlarged. The electrocardiogram is normal or at times shows left axis deviation. Clinical evidence of pulmonary hypertension is lacking and the prognosis is excellent.

Our patients showed all the features normally encountered in interventricular septal defect, but the pulmonary artery tree was dilated. The murmurs were typical and both electrocardiograms showed no axis deviation. In one, however, there was suggestive evidence for right ventricular hypertrophy in the precordial leads. In another case, recently seen by one of us and proved by post-mortem examination, there was right axis deviation and a right ventricular hypertrophy pattern in the precordial leads.[22]

The clinical importance of this entity lies in its differential diagnosis. Isolated interventricular septal defect must now be included in the differential diagnosis of congenital lesions associated with a radiographic prominence of the pulmonary artery segment. These lesions include interatrial defect, patent ductus arteriosus, Eisenmenger's complex, idiopathic dilatation of the pulmonary artery, and pulmonic stenosis with post-stenotic dilatation. The distinctive character of the murmur of interventricular septal defect is important in the diagnosis. The presence of a normal electrocardiogram is helpful in differentiating this lesion from Eisenmenger's complex and pulmonic stenosis in the absence of cyanosis, and from the majority of cases of interatrial septal defect which show right axis deviation and the right ventricular hypertrophy pattern. However, in the presence of right axis deviation and a right ventricular hypertrophy pattern which may occur in interventricular septal defect associated with a dilated pulmonary artery, the diagnosis can only be suspected. Angiocardiography and intracardiac catheterization are necessary for the accurate diagnosis.

As judged from the autopsied cases, the prognosis must necessarily be poor, since death occurred in infancy and early childhood. It is possible, however, that once survival occurs beyond infancy, the prognosis may be good.

CONCLUSIONS

1.   Isolated interventricular septal defect associated with dilatation of the pulmonary artery is presented as a clinical entity.

2.   Evidence is presented that the dilatation of the pulmonary artery may be congenital. The pulmonary sclerosis may be dependent on this factor as well as on the hemodynamic factors of a left to right shunt.

3.   The physiological data in the literature on left to right shunts are reviewed.   It is shown that there is a lack of constant relation between the calculated pulmonary blood flow, pulmonary hypertension, and pulmonary artery dilatation.

4.   The pathogenesis of pulmonary vascular sclerosis must await further physiological and anatomical correlation.

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A TECHNIQUE FOR BRACHIAL ARTERY PUNCTURE

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IN work involving the introduction of a needle into the brachial artery, the procedure was found to be so greatly facilitated by using a special section of the artery that the technique is worthy of description. Puncture of the brachial artery in the arm is made difficult by the tendency of the artery to roll, and thus it is advised in a recent text[1] that one should apply, by means of the finger, "sufficient pressure over the artery to fix its position but not to obliterate its

Fig. 1.—Needle in the lumen of the fixed section of the brachial artery.

pulsations."   At one specific point in its course down the arm, however, the
brachial artery is well fixed by the surrounding anatomical structures.   In the
antecubital fossa the brachial artery lies midway between the two epicondyles
and is covered in front by the lacertus fibrosus and the deep fascia of the arm.
About 1 cm. below the bend of the elbow the artery divides into its two terminal
branches, the radial and ulnar arteries.   In this last inch or so of its course, the
brachial artery is quite fixed in position.   The point at which the artery divides
is easily determined by palpation.   The topographical anatomy involved is
illustrated in Fig. 1.

Technique of Puncture.—Procaine is infiltrated into the skin, beginning 1 cm.
below the point where pulsations cease.   The anesthetic solution is then infil-
trated into the subcutaneous and deep tissues along the terminal section of the
artery.   The skin is punctured through the anesthetized area and the needle is
advanced proximally, toward and in line with the artery, at a 5 to 10 degree
angle with the horizontal so as to pass under the lacertus fibrosus.   The latter
structure may be perceived as a definite area of resistance should the needle
point lie too superficially.   When the artery has been entered, the needle may be
threaded up within the lumen.   The technique, as outlined, may be used with
either a regular needle or with any of the specially devised indwelling arterial
needles.

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Clinical Reports

AURICULAR FLUTTER AND COMPLETE AURICULOVENTRICULAR HEART BLOCK

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A URICULAR flutter is not an unusual condition and complete heart block is not uncommon, but the association of these two arrhythmias in the same patient is, however, very infrequent. Since the condition is rather rare and since we have seen three patients who were afflicted with it, we feel these three cases should be reported.

Jolly and Ritchie,[1] in 1911, reported the first case of this combination of arrhythmias and gave electrocardiographic proof of it.

Jourdonais and Mosenthal,[2] in 1937, described such a case and after thoroughly reviewing the literature found twenty-nine authentic cases of auriculoventricular dissociation associated with auricular flutter, their own cases being included. DiGregorio and Crawford,[3] in 1939, reported this abnormality in two male patients, one 61 years of age with arteriosclerotic heart disease and another 62 years of age in whom the abnormality was initiated by a myocardial infarct. The arrhythmias were not changed by therapy. Willius[4] encountered these combined conditions once in 40,000 electrocardiograms, while at Kings County Hospital it was noted twice in over 20,000 tracings. Since 1921 we have taken over 25,000 electrocardiograms, excluding those taken at St. Elizabeth Hospital and those sent in for interpretation. During these twenty-nine years we have seen these associated arrhythmias in three patients.

In three cases to be reported here the causative factor was arteriosclerotic heart disease and hypertension in the first, coarctation of the aorta in the second, and arteriosclerotic heart disease and hypertension in the third.

In the second patient (43 years of age) sinus rhythm was restored after administration of quinidine but a first-grade heart block persisted. In the first (73 years of age) and the third (62 years of age), the arrhythmia continued until death ensued.

These three cases, all in male patients, bring the number of patients reported to thirty-four, of which four were female and thirty were male and in which the ages varied from 13 to 74 years.

In the thirty-four cases, five had a bundle branch block (one of ours had this condition), and in only nine cases was the flutter restored to sinus rhythm (this happened in one of three cases).

To the reported cases, the following three with a summary of each are added:

CASE 1.—A hardy pioneer rancher, 78 years of age, came to our office on April 15, 1941. His past history was negative except that he had had chronic arthritis during the previous ten years for which he had been treated at various times by three different physicians, none of whom said he had any heart trouble.   The arthritic pains were principally in the back and knees, especially when rising from the sitting position.   This condition became worse during the past two weeks and his hope for relief was his reason for visiting a physician.   He had had no headache,
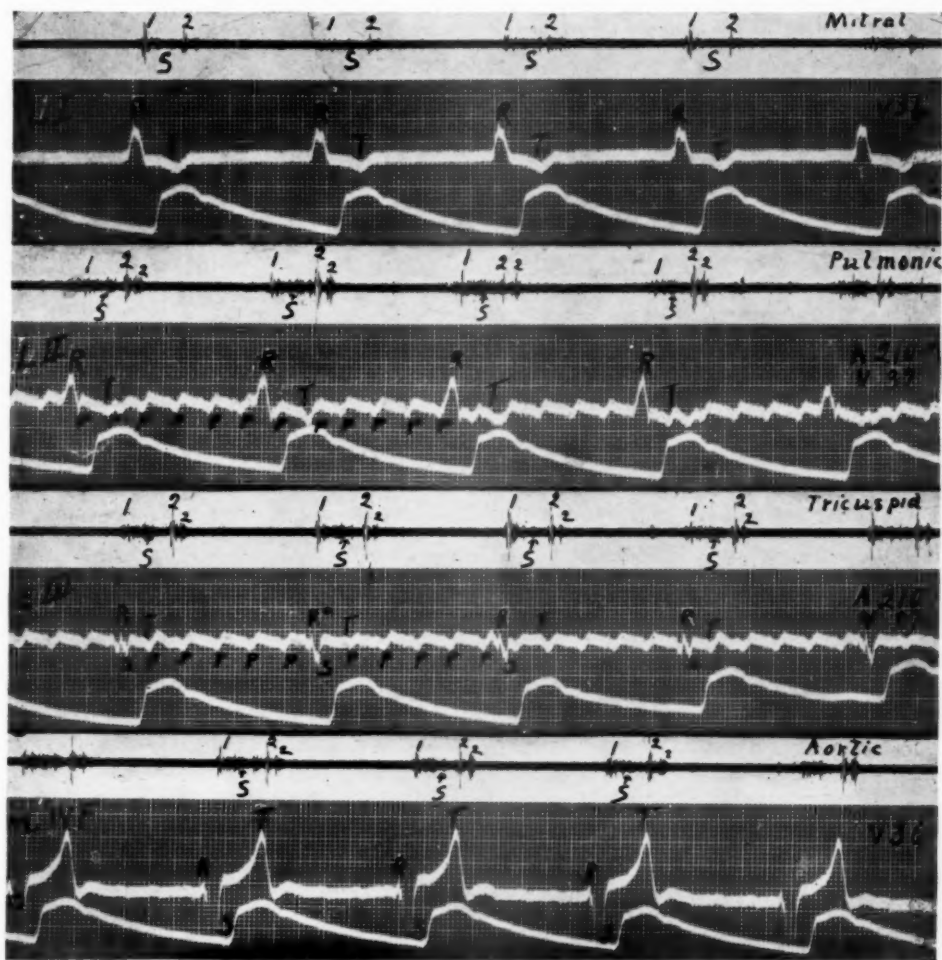
Fig. 1.—Case 1. Electrocardiogram: Auricular flutter rate 210, ventricular 37. Left bundle branch block (QRS interval is 0.14 second). The auricular flutter is shown especially well in Leads II and III.

Stethogram: Systolic (s) murmur over all valvular areas. Reduplicated second (2_2) sounds over the pulmonic, tricuspid, and aortic areas.

Polygram: The apex of each pulsation is rounded and long-sustained.

dizziness, dyspnea, edema, palpitation, precordial or substernal pain, urinary disturbances, or stomach distress, and slept well on one pillow.

Examination: The blood pressure was systolic 200 mm. Hg and diastolic 105 mm. Hg. All superficial arteries were hard and tortuous. There was no dyspnea, edema, or congestion of the superficial veins. The retinal arteries were narrow and tortuous. There were no abnormal waves

seen in the neck veins. The lungs were normal and the liver was normal in size and consistency. The leg muscles were considerably atrophied but the reflexes were normal.

The entire back was bent forward and partly fixed, especially in the lumbar area, roentgenograms of which showed a great proliferation of osseous tissue at the angles of the compressed and fused bodies.

The apex heartbeat was strong and displaced toward the left; the rate was slow and the rhythm regular. A coarse systolic murmur was heard over every valvular area. There were no diastolic murmurs. In the teleroentgenogram the greatest diameter of the heart was 17.5 cm. and the greatest intrathoracic diameter was 29 cm., while the left ventricular wall was much hypertrophied. A calcified plaque was seen in the aortic knob, while the ascending and descending parts of the aortic arch were somewhat widened.

The blood was essentially normal and the Wassermann test was negative. There was a trace of albumin in the urine; a few granular casts, and pus cells were present. The specific gravity varied from 1.007 to 1.016. The rest of the examination showed nothing abnormal.

In the electrocardiogram, complete heart block, left bundle branch block (QRS 0.14 second), and auricular flutter were seen. The auricular rate was 210 while the ventricular rate was 37 per minute (See Fig. 1).

In the stethogram a systolic murmur was present over all valvular areas; during diastole it was entirely quiet. All valvular sounds were of low intensity except the second and at times the first over the tricuspid area. The second sounds were reduplicated over all areas but the mitral.

In the radial pulse tracing, the rate was 37 and the peak of each beat was rounded and prolonged. No waves were seen in the jugular vein.

Diagnosis: Generalized arteriosclerosis, arteriosclerotic heart disease with auricular flutter, complete heart block, and left bundle branch block. Chronic degenerative arthritis.

Clinical Course: He was given large doses of several so-called coronary dilators and later quinidine sulfate 30 grains daily for seven days but no change in the auricular flutter occurred. Since he was most interested in his back, local treatments and salicylates in large doses were given to relieve the pain and spasm, and it was much improved. He received treatment for the back at longer intervals, and when his physicians last reported on May 13, 1942, the patient complained of no heart symptoms, though his blood pressure was about the same and the auricular flutter and heart block had not changed.

He died suddenly on Oct. 5, 1942, and the diagnosis was cerebral hemorrhage. No autopsy was done.

CASE 2.—This patient was 43 years old and had been a laborer in a quarry, a night watchman, a barber, and dairyman at various times. He was well before 1918 when he had influenza, and he had complained of leg weakness but no numbness since 1927. All his teeth were removed in 1935 on account of pain and swelling in the ankles. At no time before June 21, 1941, was heart disease reported by any physician, and before this period he did not complain of any abnormal cardiac symptoms. On this date he became dyspneic, developed a tachycardia and edema about the ankles. His physician gave him digitalis with some improvement, but the dyspnea and edema did not entirely disappear. Since then he had felt weak, tired, and dyspneic. He was still taking digitalis.

Examination: The blood pressure in both arms was systolic 172 mm. Hg and diastolic 70 mm. Hg. There was no congestion or abnormal pulsation seen in the veins of the neck.

In the teleroentgenogram the greatest diameter of the heart was 17 cm. and the greatest intrathoracic diameter was 27.5 centimeters. The heart was enlarged to the right and left. The heart sounds were normal except that a third sound was heard in the mitral area. The apex beat and the pulse were of slow rate with a regular rhythm. In the roentgenogram the aortic knob was absent but the ribs were not eroded. Fluoroscopically, the descending aorta appeared to be narrow.

The electrocardiogram (Fig. 2) shows an auricular flutter (auricular rate 270), complete heart block (ventricular rate 44), a low voltage of the QRS waves in the first three leads, right axial deviation, and a slurred R_{1-3}. A few extrasystoles are present. In the stethogram, the heart sounds are of normal duration with some variation in intensity, a third sound in the mitral area, and auricular sounds during the long diastoles in the tricuspid area. In the polygram, the radial

pulsations have a rounded peak.   In the jugular tracing the auricular (a) waves are synchronous with the P waves.   In the lungs, some dullness over the bases and coarse râles were heard in the same area.   The liver edge was 4 cm. below the costal margin and the abdominal aorta was difficult to palpate.   The pulsations of the femoral arteries were weak and there was some edema about
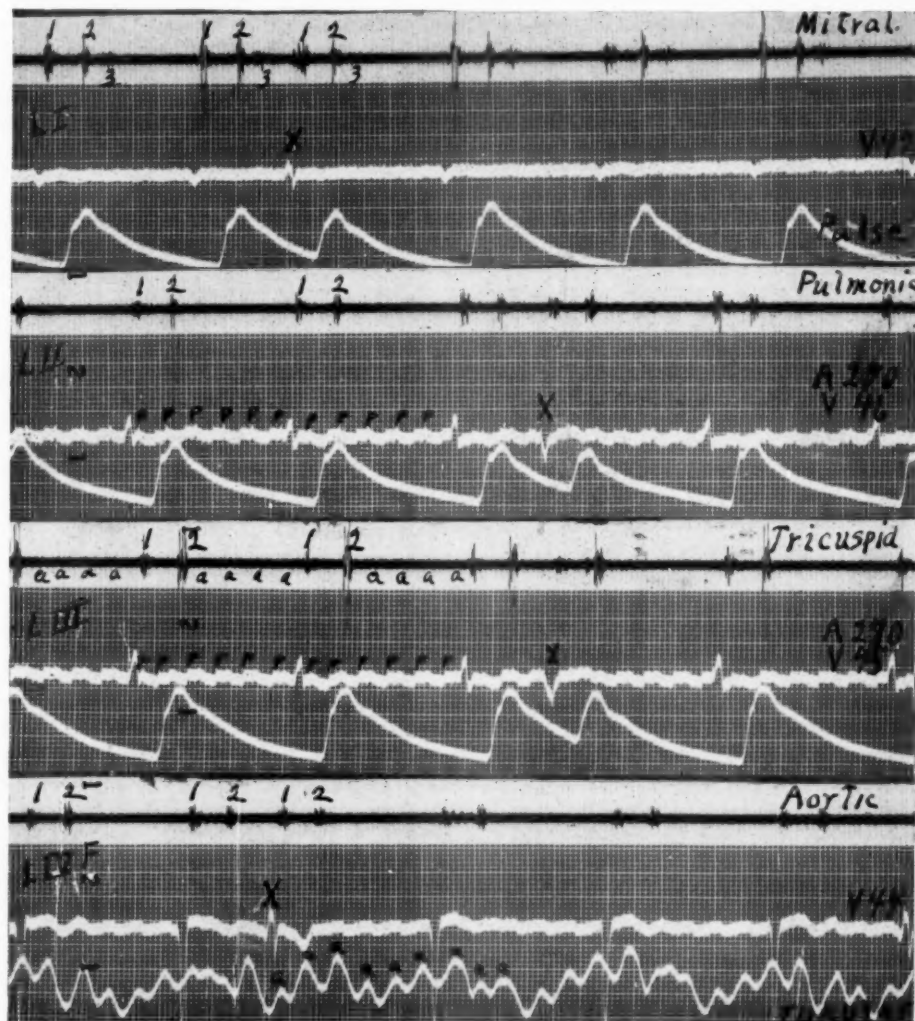

Fig. 2.—Case 2.   Electrocardiogram: Auricular flutter rate 270, complete heart block, ventricular rate 44.   Right axis deviation.   Ventricular extrasystoles (x).   Auricular flutter is clearly present in Leads II, III, and IV.

Stethogram: Heart sounds of normal intensity.   Auricular (a) sounds seen in diastole over tricuspid tracing.   Third (3) sound over mitral area.   No murmurs.

Polygram: Pulsations (radial) with rounded apex.   In jugular tracing the auricular (a) contractions are of the same rate as the P waves in the electrocardiogram.

the ankles.   No patellar reflex could be elicited, while the other reflexes were normal.   Blood examination showed leucocytes, 7,200; erythrocytes, 4,950,000; hemoglobin, 16.5 grams.   Wassermann reaction was negative.   On the spinal fluid, pressure, cells, globulin, colloidal gold, and Wassermann tests were negative.   Urine showed a slight trace of albumin, but was otherwise normal.

Diagnosis: Cardiac decompensation with auricular flutter and complete heart block.

Comment: Since he had been taking digitalis, it was thought that this drug might have been the cause of the complete heart block.   Therefore the digitalis was discontinued for three weeks but the heart block continued.   He was then given 10 grains of quinidine sulfate three times a day
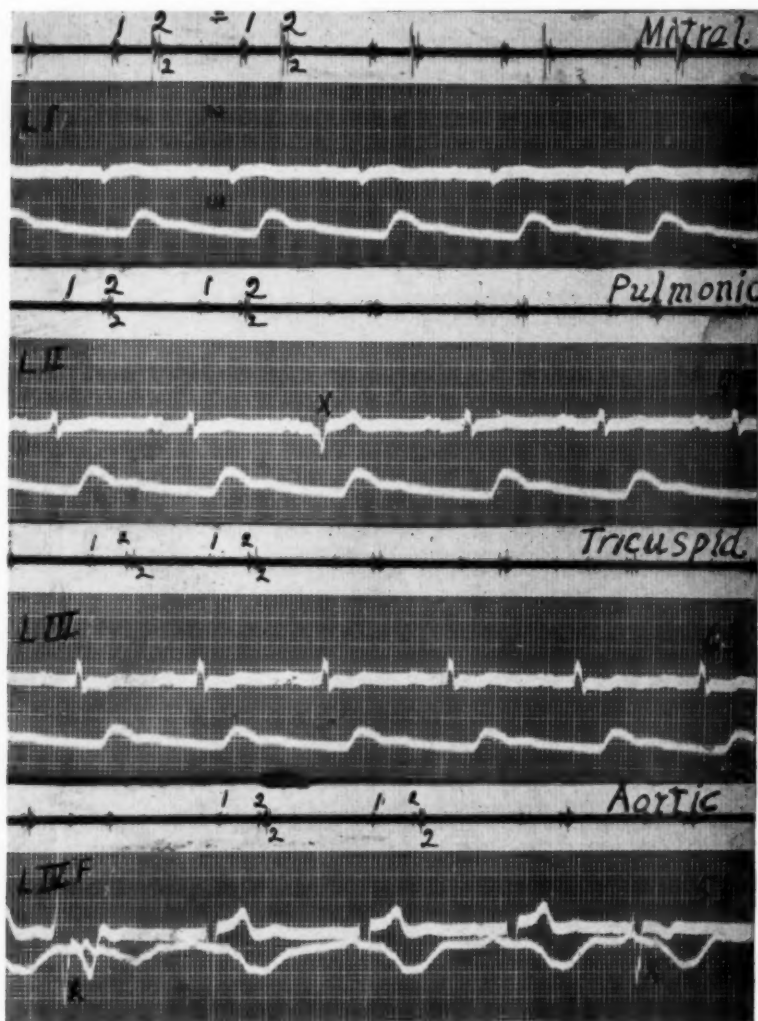

Fig. 3.—Case 2.   May 17, 1942.   Electrocardiogram: Right axis deviation, low voltage, notched P_1.   First-grade heart block (P-R interval is 0.32 second).   Depressed R-T $_3$ and biphasic T $_3$.   Auricular rate 55 to 63, ventricular rate 55 to 63.

Stethogram: All sounds of low intensity except mitral second (2).   No murmurs.   Reduplicated second (2_2) sound over all valvular areas.

Polygram: Normal except for extrasystoles.

and on the seventh day, when 190 grains had been taken, sinus rhythm was restored.   At this time the heart rate averaged 62 per minute.   In the electrocardiogram (Fig. 3) the P-R interval is 0.26 second while the same low voltage and the right axial deviation continue.   A few extrasystoles are present.

Last Examination: April 17, 1942. He still complained of some dyspnea, leg weakness, and numbness. He had taken quinidine, 5 grains each day since the sinus rhythm developed. The systolic pressure was 145 mm. Hg; diastolic, 60 mm. Hg.

The roentgenogram showed the heart to be smaller, the greatest diameter being 15 cm. and the greatest intrathoracic diameter 27 centimeters. The principal decrease was in the right heart, the left being hypertrophied. The descending aorta could not be seen. No murmurs but a few extrasystoles were heard. The electrocardiogram revealed low voltage, right axial deviation, notched P_{2-3}. The P-R interval was 0.32 second, depressed $R-T_3$ and biphasic T_3 and ventricular extrasystoles. The rate was 55 to 63.

We have not seen the patient since this date. His physician has reported his having had cardiac decompensation several times but these attacks always responded to digitalis. The heart rate has never been slow but it has always been regular except for some extrasystoles.

Conclusions: It may be possible that digitalis caused the complete heart block, and had we waited longer, sinus rhythm might have returned spontaneously. However, we know he had taken quinidine, grains 5, for ten months after sinus rhythm was restored. We do not know whether he had taken it since then or not.

CASE 3.—This patient was a man aged 62 years who had been fairly well until three months previous to admission when he noticed he was dyspneic. He was taking cactus, so he said, during this period of time, but the dyspnea gradually increased until he developed severe orthopnea and could only sleep sitting in a chair during the two weeks prior to admission. Substernal pressure developed when walking and this was relieved by rest. He had had ankle edema for about four weeks and Cheyne-Stokes respiration for about two weeks. He was constipated and urinated three to four times at night.

Examination: Blood pressure was systolic, 180 mm. Hg; diastolic, 120 mm. Hg. Severe dyspnea with Cheyne-Stokes respiration was present. Superficial arteries were hard and tortuous. The neck showed no congestion in the jugular veins. The heart was enlarged to the left, rate 112, sinus rhythm with some premature systoles. Valve sounds were distant but no murmurs were heard. In the teleoroentgenogram the heart was enlarged to the left, the greatest cardiac diameter was 19 cm. and the greatest intrathoracic diameter was 33 cm. The aorta was elongated but of normal width. Dullness and coarse râles were noted in both bases of the lungs and each base in the roentgenogram was hazy. The liver was palpated 6 cm. below the costal margin and was tender to pressure. Edema was present about the ankles. Blood examination revealed leucocytes, 12,300; red cells, 5,200,000; and hemoglobin, 106 per cent. The Wassermann test was negative. Urine specific gravity was 1.022, albumin one plus, a few granular casts. An electrocardiogram showed sinus tachycardia and left ventricular hypertrophy.

Diagnosis: Generalized arteriosclerosis. Arteriosclerotic heart disease with hypertension. Congestive heart failure.

Clinical Course: Ouabain 0.5 mg. intravenously, folia digitalis 6 grains orally, and Salyrgan, with theophyllin 2 c.c. intravenously, were administered. In two hours the heart rate was 66 and the respiratory rate was normal. In four hours he had passed 1,150 c.c. of urine and felt very comfortable.

Following this, folia digitalis 1½ grains daily was given as needed. From this time until June 27, 1946, he had varying periods of dyspnea, substernal pressure, and edema. At various times papaverine, Glucophylline, aminophylline, digitalis, and Salyrgan were given. His physician informed us the patient did not follow his diet and took the drugs prescribed as he pleased.

On June 27 he was edematous, dyspneic, and complained of substernal pain. Blood pressure was: systolic, 140 mm. Hg; diastolic, 95 mm. Hg. The liver was tender and was palpated 5 cm. below the costal margin. The heart was dilated to the left, a systolic murmur at the apex was heard, and the rate was slow but regular. The electrocardiogram (Fig. 4) showed complete heart block with auricular flutter and right axis deviation. The auricular rate was 288 and ventricular rate was 41. It was suggested that he probably had a myocardial infarct but the electrocardiographic findings did not confirm this.

He was hospitalized July 1, and given Salyrgan (intravenously), 1,000 c.c. of fluid by mouth, and a low salt, low protein diet, and in twelve days the edema had disappeared and he was sent

home. Quinidine was given 40 grains a day for seven days and was then discontinued. No change in the rhythm was noted.

After he went home the edema reappeared. He was hospitalized three times when very edematous and each time the edema disappeared. However, the combined complete heart block and auricular flutter continued.
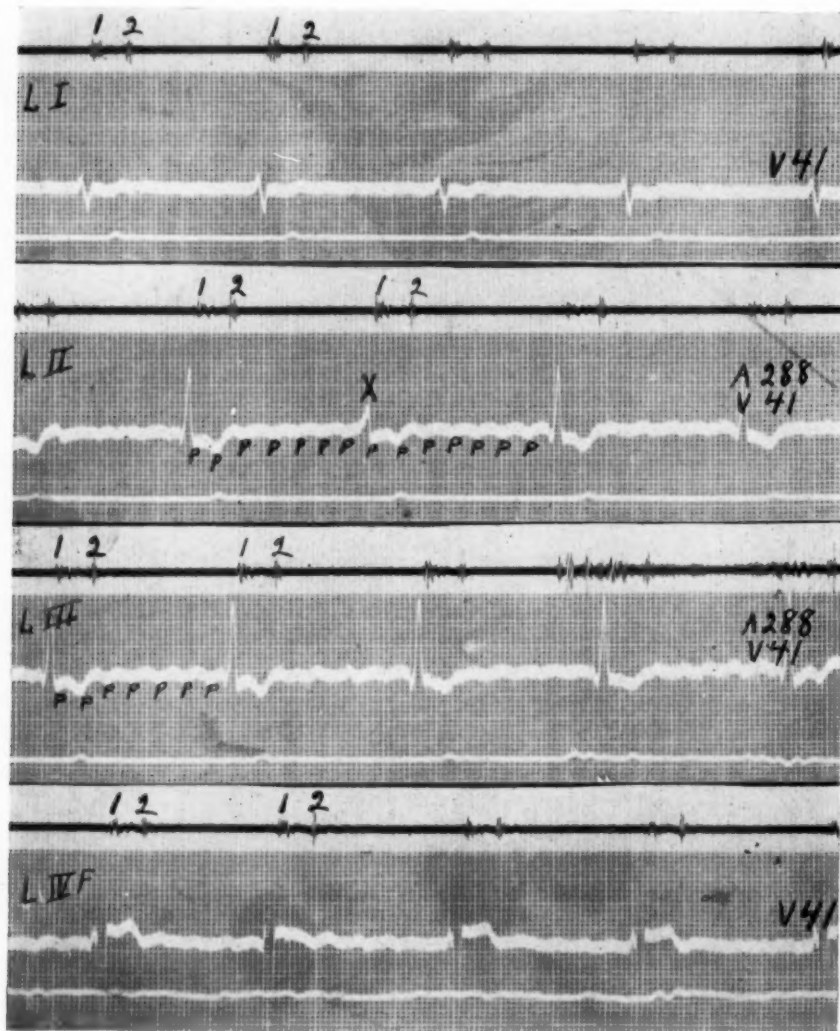

Fig. 4.—Case 3. June 27, 1946. Electrocardiogram: Auricular flutter rate 288, complete heart block, ventricular rate 41.

Stethogram: All sounds of low intensity. No murmurs.

Polygram: Low volume.

He died at home on March 9, 1947. His physician said he was very edematous and that his heart rate was never above 40 per minute.

COMMENT

As far as medical literature is concerned, combined auricular flutter and complete heart block is a very rare condition.   In the cases reported a high percentage of the patients afflicted are over 50 years of age.   This is to be expected since most of those suffering from these associated conditions had primarily arteriosclerosis, arterial hypertension, and coronary artery disease.

Two of our patients had these associated conditions when first seen and one developed them during treatment.   We do not believe digitalis was a causative factor in our cases but most probably progressive arteriosclerosis was the cause. One also had a left bundle branch block.   All of our patients received quinidine but in only one was sinus rhythm restored.   In this patient a first-grade heart block continued until we lost track of him.

The prognosis in this condition is probably about the same as in uncomplicated complete heart block of arteriosclerotic origin.   After the discovery of the combined conditions, the first of our patients lived about eighteen months and died of cerebral hemorrhage, the second was followed ten months but the outcome is not known, and the third died of congestive heart failure in about nine months.

The diagnosis can be suspected clinically in a slow, regular heart and observation of rapid regular waves in the jugular veins, but can be definitely made only by electrocardiogram.

SUMMARY

Three cases of associated auricular flutter and complete heart block are reported.   One patient also had a left bundle branch block.

In one patient sinus rhythm was restored but a first-grade heart block followed, while in two the abnormal rhythms continued until death.

The basic causative factor was most probably arteriosclerosis.

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PARADOXICAL GANGRENE FOLLOWING LUMBAR SYMPATHECTOMY

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THE development of acute gangrene following lumbar sympathectomy is a dramatic complication which remains incompletely understood. An attempt has been made, in the past, to explain the development of such gangrene on the basis of arteriovenous shunts.[1-3] The proponents of this theory feel that sympathetic paralysis results in a general opening of arteriovenous shunts which produces a by-pass of the capillary bed, further reduces oxygenation, and finally results in gangrene.[4,5] Although this theory is based on demonstrable anatomical facts, it still leaves much to be desired in the explanation of the actual course of events in such patients. We have recently studied a patient in whom the clinical course and subsequent autopsy examination suggested that factors other than arteriovenous shunts may produce gangrene in postoperative sympathectomized individuals.

Perhaps one of the greatest fallacies in thinking on the subject of arteriosclerotic gangrene is in considering the disease as solely a mechanical problem of narrowing arterial lumina. The narrowing of the lumen of an artery by arteriosclerosis is a pathological fact which can readily be demonstrated by dissection at the autopsy table. It is also readily demonstrable that the narrowed lumen is accompanied by changes in the vessel wall which may involve the intima in an ulcerative process. What seems to be less frequently appreciated is the fact that the pathological changes in the artery are associated with changes in its contents, so that thrombosis in the diseased arteries is rather common and probably precipitates the attack of gangrene. Arteriosclerotic gangrene, then, is better considered to be not merely the result of a mechanical interference with the blood supply but rather an expression of a thrombotic process superimposed upon the mechanical narrowing of the arterial lumen. We will attempt to demonstrate in this communication that the logical treatment of arteriosclerotic gangrene necessarily includes a biphasic approach, treating not only the mechanical obstruction but also the tendency toward thrombosis.

The fact that thrombi are inconstantly found in the large vessels of limbs amputated for ateriosclerotic gangrene does not preclude their presence higher in the vessel. The site of amputation is almost always below the point of occlusion. Furthermore, if ulceration or gangrene is present, a second, easily demonstrable source of thrombosis can be postulated. The gangrenous extremity can,

therefore, be expected to have a thrombotic occlusion at a high level in the arterial tree, which is the precipitating factor, and, in addition, there is secondary thrombosis of the vessels (arteries and veins) in the region of the gangrene or ulcer. Both of these areas of thrombosis, like any thrombus, are prone to growth by extension. In a limb whose vascularity is already compromised, such propagating thrombi will readily produce gangrene if they extend to involve collateral arteries. The patchy and unpredictable course of the gangrene is due to the fact that the propagating thrombus may be either peripheral or central. The sequence of events can be outlined as follows:

1. Arteriosclerosis is accompanied by intimal damage.
2. Pathological changes of the arterial intima, when severe, will precipitate thrombotic occlusion.
3. Surgical procedures (sympathectomy) will further increase the coagulability of the blood.
4. Increased coagulability of the blood will predispose to propagation of the thrombi already present.
5. Propagation of a thrombus along a diseased vessel will result in gangrene when collateral arteries are occluded.

CASE REPORT

E. M. R., a 58-year-old, white male patient, was admitted to the hospital March 3, 1949, for treatment of chronic ulceration of the toes of both feet and of the medial aspect of the left knee and for arteriosclerotic heart disease. This man had had arteriosclerosis for years. He had an attack of coronary heart disease in 1928, and had been receiving a government pension since 1948 for arteriosclerotic heart disease with myocardial damage, coronary occlusion, and anginal syndrome. His chief complaint on admission, March 3, 1949, was the presence of recurrent ulcers on his toes, which were slow in healing. He also had an ulcer on his left knee. In addition, he complained of pain in the calves of his legs which was aggravated by standing and walking. Since 1928 he had been experiencing mild anginal attacks, which averaged about two a week but were not incapacitating. He was examined completely by the Veterans Administration approximately one year previous to admission, at which time the diagnosis of diabetes was eliminated and a diagnosis of arteriosclerotic heart disease established. He had been working as a bank clerk without too much difficulty from his disease.

Physical examination revealed a thin but well-nourished white man who did not appear to be ill and who seemed younger than his stated age. Examination of the head and neck revealed nothing abnormal. The chest was normal to inspection and palpation and resonant on percussion. No adventitious sounds were heard on auscultation. The heart was questionably enlarged. The rhythm was regular but the tones were of poor quality. No murmurs were heard. The blood pressure was 115/65 mm. Hg, and the pulse was 70. The abdomen was flat and soft. Rectal examination was negative.

Examination of the legs revealed a punched-out appearing ulcer 2 cm. in diameter present over the tip of the left great toe. A somewhat larger ulcer was present on the medial side of the left knee. Smaller ulcers were found on the web between the fourth and fifth toes. It was noted that when the feet were dependent they became cyanotic and when elevated they blanched. The femoral pulse was absent on the left and present on the right. The distal pulses were present on the right although diminished in quality. Distal pulses were not palpable on the left. A diagnosis was made of (1) generalized arteriosclerosis, (2) arteriosclerotic heart disease, (3) arteriosclerotic, occlusive, peripheral vascular disease with impending gangrene of the left lower extremity.

Roentgen examination of the chest revealed normal lung fields with some evidence of an old pleuritis in the left base. The heart was moderately enlarged, occupying about 52 per cent of the diameter of the lower chest. Left ventricular hypertrophy was noted.

A routine blood count revealed 4.6 million red cells, 5.5 thousand white cells, 13.5 Gm. of hemoglobin and a normal differential count. The Wassermann test was negative, and a urinalysis was normal. Chemical analysis of the blood revealed a fasting level of 302 mg. per cent of sugar and nonprotein nitrogen of 35.5 mg. per cent.

It was felt that a mild degree of diabetes was present, and he was accordingly treated with regular insulin. However, with dietary control it became obvious that insulin was not needed. A second blood sugar revealed a level of 86 mg. per cent and his urine remained sugar-free without insulin. Because of the vascular disease a left lumbar, paravertebral, sympathetic block was performed on March 3, 1949. A questionable amount of relief was obtained.

On March 9, 1949, a left lumbar sympathectomy was done. A muscle-splitting incision was used, and the second, third, and fourth sympathetic ganglia were removed. The operation was easy, uncomplicated, and took thirty-eight minutes. The patient was returned to the ward in good condition but that afternoon began complaining of pain in his right leg. Histologic section of the tissue removed showed normal nerve fibers with no degenerative changes and numerous ganglion cells. The pathological diagnosis was sympathetic ganglion and nerve trunk.

Physical examination on the afternoon following operation revealed the right leg to be cold and covered with a blotchy cyanosis. The femoral pulse was now absent bilaterally. A right lumbar paravertebral block was done without relief of symptoms. Because of the acuteness of the onset, a diagnosis of possible embolism in the right iliac artery was made. Since the onset was so recent and the prognosis so grave, it was felt that embolectomy was indicated even though the fact that a thrombosis might be present was appreciated.

Accordingly, that afternoon the patient was operated upon. Local anesthesia was used. A longitudinal incision was made over the femoral vessels. These vessels were identified, and the artery was isolated and opened. The opened artery was found to be extremely arteriosclerotic and empty, containing neither blood nor thrombus. Attempts were made to pass a small-sized rubber catheter up the artery, but they failed because of its extreme stenosis. A small, flexible probe was passed upward into the iliac artery, and when it was withdrawn a small trickle of blood was returned but no actual bleeding occurred. A small-sized suction tube was passed into the iliac artery, but still no thrombus could be removed and no bleeding could be produced. It was finally decided that these efforts were in vain and it was felt that division of the femoral vessels was indicated in order to interrupt any vasospastic reflexes which might be present. Therefore, the artery and vein were divided and individually ligated.

The experience at the operating table made the diagnosis of propagating arterial thrombus the most likely one and intensive anticoagulant therapy and penicillin were immediately started. He was given 300 mg. of heparin in Pitkin's menstruum intramuscularly and 300 mg. of Dicumerol by mouth. Fifty thousand units of penicillin were given every three hours.

On March 10, 1949, the first postoperative day, the right lower leg was cold and was showing signs of early gangrene which extended well up into the thigh. The left leg was approximately the same as before operation. Severe pain was present in both extremities. The pulse was 120 at this time. A gangrenous area appeared on the scrotum and was considered to have serious prognostic implications. It was felt at this time that the right leg was definitely lost up to the upper third of the thigh but hopes were still sustained for the left. The prothrombin time was increased to twice that of the control and maintained at this level. The coagulation time could not be raised above five and one-half minutes. The patient gradually failed and on the eleventh of March it became obvious that the gangrenous process was beginning to involve the left leg as well as the right. His abdomen became distended, and he vomited coffee-ground material. A serosanguineous discharge was passed per rectum, suggesting that the thrombosis had extended up the aorta to above the inferior mesenteric artery. The prognosis at this time became hopeless, his condition being such that any further surgical interference was out of the question. A nasogastric suction tube was inserted, and he was treated symptomatically. He gradually lost ground and expired on March 15, 1949. At the time of his death the gangrene had involved the left leg to below the knee and the right leg to the hip.

Autopsy.—A post-mortem examination was done and revealed a thrombus to be present in the abdominal aorta which completely occluded its lumen from a point just distal to the ostia of the renal arteries down into the left external iliac artery. The part of the thrombus in the left common and external iliacs showed evidence of organization. The clot above this extending upward into the abdominal aorta was deep red, firm, and obviously of more recent origin. The thrombus extended down the right iliac only as far as the bifurcation. All of the branches of the aorta below the renal arteries were, therefore, occluded. As a result the gangrenous process involved not only the lower extremities but also the sigmoid colon, urinary bladder, and scrotum. There was gross evidence of myocardial damage including an aneurysm of the anterior wall of the left ventricle. There was narrowing of the anterior branch of the left coronary artery in the region of the aneurysm.

Histologic sections of the iliac artery revealed advanced arteriosclerosis on which was superimposed an organizing thrombus which occluded the lumen. The intima of the wall was greatly thickened. The lower part of the intima showed fatty degeneration with large aggregations of cholesterol crystals. In some areas calcification was seen. The organized thrombus was densely adherent to the wall of the vessel and many fibroblasts were seen extending into it.

DISCUSSION

The patient described above represents a case of generalized arterial degeneration complicated by intra-arterial thrombosis with a fatal outcome. The fact that the thrombus in the left iliac artery was old was substantiated by histologic examination which revealed fibroblastic organization. Postoperative propagation of the thrombus centrally resulted in occlusion of the right iliac artery and subsequent gangrene of the contralateral extremity. Gangrene of the scrotum suggested bilateral occlusion of the hypogastric arteries, and a bloody discharge from the rectum indicated gangrene of the bowel due to occlusion of the inferior mesenteric artery. The sudden onset of this chain of events immediately following operation would lead one to suspect that the operation played a precipitating role. The most likely way by which an operation might precipitate a propagating thrombus would be by increasing the coagulability of the blood. It is possible that if this patient had been given heparin before and immediately after operation the propagation of the thrombus would have been avoided or inhibited. The recommendation is, therefore, that patients with arteriosclerotic gangrene be given anticoagulant therapy preoperatively and intensively in the postoperative period. This technique should be followed in cases where gangrene is present as well as in cases where impending gangrene may be feared. It is probably wise to use anticoagulant therapy preoperatively and postoperatively in all cases considered for lumbar sympathectomy for arteriosclerosis.

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CONGENITAL HEART DISEASE IN OLD AGE

Interauricular Septal Defect With Mitral and Tricuspid Valvulitis

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THE growing importance of accurately diagnosing congenital malformations of the heart during life has led to the realization that such disorders may be the cause of heart disease in relatively advanced age. Of these, defects in the development of the intra-atrial septa are well known to be compatible with longevity.[1-3] The case of an 82-year-old woman who died in congestive heart failure occasioned primarily by a widely patent interauricular communication and complicated by a healed rheumatic mitral valvulitis (Lutembacher's syndrome) is presented because the patient appears to be the oldest subject reported with this syndrome and because the anatomical findings allowed an unusually clear insight into the embryology of the developmental defect. The life history of the patient, which included five pregnancies and a successful outcome of a major operation when she was 79 years old and in obvious congestive heart failure, is of added interest.

CASE HISTORY

Mrs. Y. B., a 79-year-old Dutch housewife, was first seen in 1944 when she entered the surgical service because of a sudden onset of right lower quadrant pain ten days prior to admission and continued discomfort since that time. She had been well all her life except for increasing shortness of breath during the past five years for which she had taken digitalis at irregular intervals. She had borne three children without difficulties and knew of two spontaneous abortions.

Physical examination revealed diffuse abdominal tenderness, somewhat more pronounced in the right lower quadrant, with pain on rebound. The heart appeared enlarged to the left anterior axillary line, the rhythm was totally irregular, varying between 200 and 250 beats per minute. Apical systolic and diastolic murmurs were audible. The blood pressure measured 134/78 mm. Hg. No râles were heard over the lungs, and the liver was barely palpable at the rib margin. There was no edema. The diagnosis of a perforated appendix was made and a laparotomy was performed. An acutely gangrenous appendix was removed and an appendiceal abscess was drained. Following the operation, the patient made an uneventful recovery. Under intensive digitalis medication the heart rate fell during her hospital stay to below 100 beats per minute but remained irregular.

The patient was next seen on the medical service three years later, in 1947, when she complained chiefly of recurrent pain in the right upper abdominal quadrant associated with nausea and vomiting which had occurred with increasing severity over a period of three months. The dietary history and the recent complaints suggested an acute exacerbation of chronic gall bladder disease although a cholecystogram demonstrated a normally functioning gall bladder. A gastric analysis revealed 14 units of free acid after histamine with 29 units of total acid. Again the

heart appeared enlarged.   No abnormal pulsations could be felt, but a systolic thrill was palpated along the left sternal border and over the apex.   A loud (Grade III) systolic murmur could be heard with maximal intensity over the apex which lasted throughout systole and was transmitted upward along the sternum and laterally into the axilla.   The second pulmonic sound was accentuated and in the left lateral position a well-localized, early diastolic rumbling murmur was easily noted over the apex.   The rhythm was irregular and ranged around 200 beats per minute.   The blood-pressure measured 145/100 mm. Hg.   Bilateral corneal opacities prevented the visualization of fundi.   No râles were noted over the lungs, the liver was not palpable, and no edema was noted.   An enlarged, firm, non-nodular thyroid was palpated but no signs and symptoms of hyperthyroidism were present.

Fig. 1.—Chest x-ray. Note prominent pulmonary artery and increased pulmonary vascular markings.   The film was obtained during the first admission to the medical department and four weeks prior to death.

An x-ray of the chest revealed marked cardiac enlargement in all diameters with an extraordinary prominence of the pulmonary artery.   On fluoroscopic examination accentuated pulsations were noted in this region (Fig. 1).

Numerous electrocardiograms were obtained.   All revealed evidence of right bundle branch block in a vertically placed heart.   Auricular flutter was present throughout with a ratio of auricular to ventricular responses varying from 1:1 to 4:1.   A 2:1 auricular flutter was the most common irregularity (Fig. 2).

The patient was redigitalized with 1.2 mg. of Digitoxin* and maintained on 0.2 mg. Digitoxin per day without appreciable benefit.   An attempt to restore a normal sinus mechanism failed because, following a total dose of 1.4 Gm. of quinidine sulfate over a forty-eight-hour period,

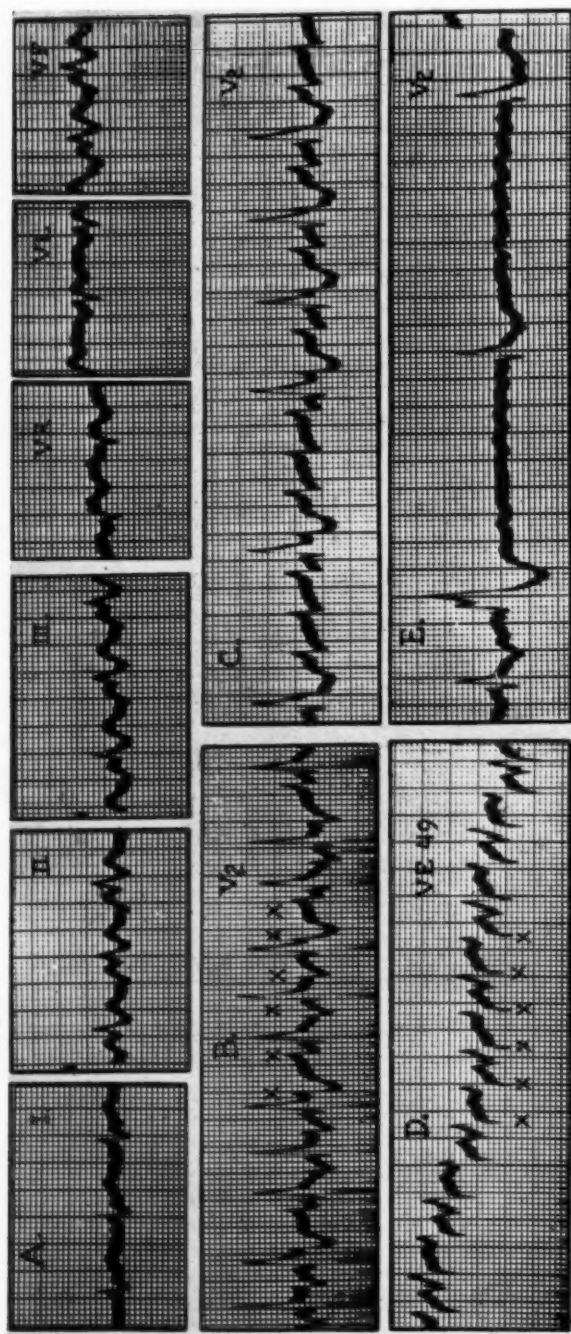*Supplied by the courtesy of the Lakeside Company.

Fig. 2.—Electrocardiograms obtained over a six-week period. A, Leads I, II, III, V_R, V_L, and V_F on first admission to the medical department, November 14. B and C, Unipolar precordial Lead V_2, B taken November 20, and C taken December 2. D, Unipolar esophageal lead with tip of electrode 40 cm. from tip of tongue, November 20. E, Unipolar precordial Lead V_2, December 30.

Twelve leads were always recorded on these and other occasions but only representative examples have been selected for illustration.

Right bundle branch block was always present as indicated by broad S waves in Lead I (A), late R waves in Lead V_R (A), and delay in the onset of the intrinsicoid deflection in Lead V_2 (B, C, and E). A 2:1 auricular flutter was noted on admission (A), flutter with irregular ventricular responses (1:1, 2:1, and 4:1) were observed (B, C, and D) before auricular fibrillation had occurred (E) presumably as the result of digitalis therapy.

The esophageal leads (D) demonstrated the coordinate excitation of auricular muscle characteristic of auricular flutter. (x indicates auricular complexes.)

the patient developed severe nausea and vomiting.   An erythematous rash appeared over the trunk and extremities which rapidly progressed and began to exfoliate.   It subsided under therapy before discharge.   The fundamental cardiac rhythm could not be altered by quinidine but persistent digitalization maintained a higher degree of auriculoventricular block so that the patient was discharged after twenty-six days of hospitalization with a ventricular rate of 70 beats per minute.

She was readmitted three weeks later complaining of extreme shortness of breath and general weakness.   The patient now appeared to be in congestive failure and was definitely obtunded. The physical findings over the heart were unchanged except that the heart rate, still irregular, ranged at 65 beats per minute.   Fine and coarse râles were now heard over the entire lungs, and soft pitting edema was present over the lower extremities.   Moderate cyanosis was seen and the veins were distended.   The liver was not palpable.   The electrocardiogram now revealed right bundle branch block, occasional ventricular extrasystoles, and auricular fibrillation (Fig. 2). The patient could be aroused only with difficulty and died in spite of intensive treatment thirty-six hours after admission.

An autopsy performed seven hours after death demonstrated a normal biliary system and a chronic perforating ulcer on the posterior wall of the stomach, eroding the head of the pancreas.

The thyroid gland was enlarged and contained colloid nodules.   The pulmonary artery was moderately dilated, measuring 11 cm. in circumference 2 cm. distal to the valve ring.   A 1 by 2 by 1 cm. parietal thrombus was attached to the left pulmonary artery over an atheromatous plaque which encroached upon the lumen.   Arterial branches to the upper and lower lobes of the left lung and to the upper lobe of the right lung were occluded by thrombi.   Hemorrhagic infarcts and confluent bronchopneumonia involved the left lower lobe.

The heart was situated in the thoracic cage in a transverse position with the apex pointing directly to the left.   It was rotated so that the medial wall of the right ventricle formed the left cardiac border.   It weighed 525 grams.   There were many discrete and coalescent petechial hemorrhages throughout the epicardial fat.   There was a 2 by 3 cm. smooth, gray opacity of the epicardium of the left auricle.   The coronary arteries revealed moderate atheroma.   The endo-cardial surfaces of all chambers were glistening, smooth, and pale red.   The right auricle was markedly dilated and was estimated to have about three times the capacity of the left auricle. The pectinate muscles of the right auricle were moderately hypertrophied.   The right ventricle was markedly dilated and was estimated to have a capacity of about twice that of the left ven-tricle.   The maximal thickness of the right ventricular myocardium was 6 mm.   The left ven-tricle was small, and the myocardium measured 12 mm. in thickness near the base and 9 mm. near the apex.   The myocardium showed no evidence of degeneration or scarring.   The circum-ference of the pulmonic valve ring was 8 cm.; of the aortic, 7.5 cm.; and of the tricuspid, 14 cm. The mitral valve ring measured 9 cm. in circumference.   The mitral leaflets demonstrated only nodular fibrosis.   The leaflets of the tricuspid valve were diffusely fibrotic, showed nodular thick-ening of the free margins, and failed to completely close the orifice.   The chordae tendineae of the mitral and tricuspid valves were slightly thickened, and the tips of the papillary muscles were fibrotic.   The pulmonic cusps were approximately twice normal thickness.   The aortic valve cusps showed slight atheromatous degeneration.

The aorta was less than 2 mm. in thickness and showed moderate atheroma without calcifica-tion or ulceration.

In the interatrial septum there was an oval defect 2.5 by 3.5 cm. in diameter, occupying approximately one-half of the area of the septum (Figs. 3 and 4).   There was no structure on the cephaloventral surface of the atrial wall at the site of the defect which would suggest the presence of an interatrial septum.   In this area the endocardium of the two atria was smooth and con-tinuous.   Along the dorsal and ventral margins of the defect there was a thin, fibrous structure representing the interatrial septum.   The inferior margin was slightly thickened, smooth, and rolled.   The remnant of the septum inferior to the defect measured 2 by 3 by 9 mm.   Traversing the center of the defect was a gray, paper-thin, fibrous band 1 cm. in width.   There was a second thin, narrow, fibrous strand which measured 1 by 11 mm. along the inferior border at the posterior limit of the defect.

In summary, the examination of the heart demonstrated the presence of a large interatrial
septal defect associated with fibrosis of the mitral and tricuspid leaflets, moderate dilatation of
the pulmonary artery, and right auricular and ventricular dilatation and hypertrophy.
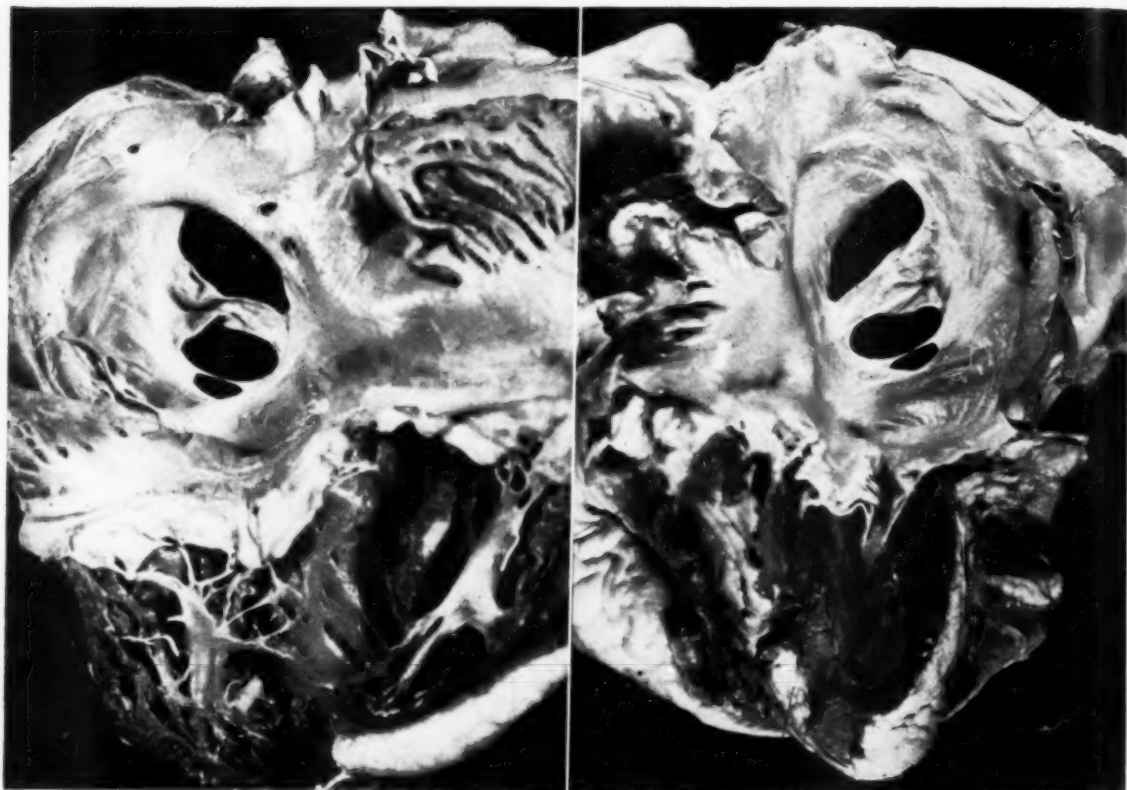
Figs. 3 and 4.—Open intra-atrial communication as viewed from the right (Fig. 3)
and from the left (Fig. 4) atrium (See text).

DISCUSSION

A brief synopsis of the embryology of the atrial septa allows a number of
conclusions concerning the type of defect in this patient. The common primitive
atrium is divided into the two chambers by a septum (septum primum) which
during the second month of gestation grows from the upper posterior region of the
common atrium toward the as yet undivided atrioventricular ring. Endocardial
cushions grow at this time from the lower anterior and posterior regions of this
ring and divide the common atrioventricular canal into two separate atrio-
ventricular openings. For a short time after this division has taken place a
communication still exists between the two atria because the septum primum has
not yet met and fused with these endocardial cushions (foramen primum) (Pat-
ten, after Born and Tandler[4,5]). As the foramen primum closes, another opening
gradually develops in the upper posterior portion of the septum. It first appears
as a cribriform structure with several perforations and finally enlarges to a single

orifice (foramen secundum—Born). At this time a second septum appears to the right of septum primum. Its crescent-shaped growth divides the atria again into two auricles except for a characteristic ovale lumen at the upper posterior
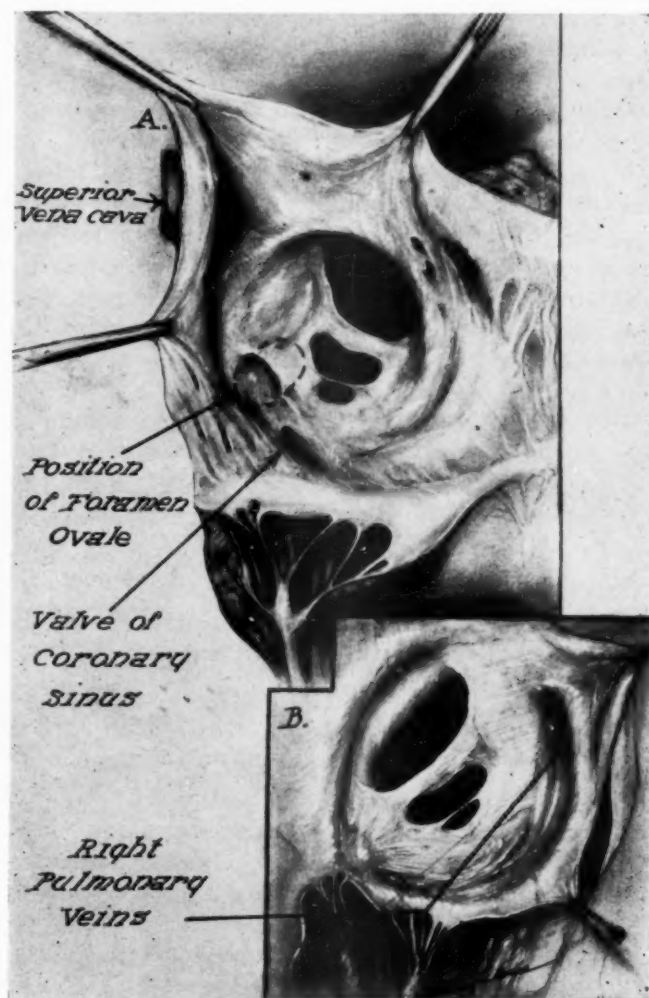

Fib. 5.—Anatomical drawing of the atrial defect representing persistence of the interatrial foramen secundum. The membrane separating the two auricles represents the septum primum. The lower border of the defect in the vicinity of the coronary sinus may represent a part of septum secundum (See text.) A corresponds to Fig. 3; B to Fig. 4. (Drawing by Mrs. Helen Cleare Cartwright).

regions, the adult foramen ovale. Remnants of the septum primum not ultimately fused with septum secundum remain to form a valvelike closure over the foramen ovale (valvulus foraminis ovalis). Minor differences in the development of the openings in septum primum and in the development of septum secundum suggested by Odgers[6] are of no particular concern for the present discussion.

A close inspection of the defect in the interauricular septum of the heart under consideration (Fig. 3) allowed the following assumptions: The septum primum had developed normally and had closed the interatrial foramen primum. The interatrial foramen secundum was present. The posterior (intact) one-half of the interatrial septum represented septum primum which normally persisted to form the valvulus foraminis ovalis. The anterior, perforated half represented that part of the septum primum that had persisted after the cribriform perforation (foramen secundum) had developed and enlarged. Septum secundum apparently failed to develop to a degree recognizable at death, or, less likely, developed incompletely and then regressed until no vestige resembling the annulus fossae ovalis could be recognized. A fibrous ridge along the inferior margin of the septum primum in close relation to the atrioventricular valves was present. This structure measured 2 by 9 mm. and extended the length of the septum between dorsal and ventral walls of the atria. It marked the inferior border of the abnormal orifice through the septum primum. Whether this ridge represented the ventrocaudal limb (Patten) of septum primum or the ventral mass posulated in Odgers' theory of origin of the septum secundum, seems unimportant. Its presence, however, did suggest that at least part of the septum secundum was represented (Fig. 5).

The defect obviously did not represent a persistent foramen primum because (a) a fibrous ridge separated the two auricles at the point of closure of the original atrioventricular endocardial cushions; (b) the atrioventricular openings and the valve leaflets showed no evidence of malformation; and (c) the abnormal communication between the right and left atrium was located above and posterior to the expected location of a foramen primum.

Right auricular and ventricular hypertrophy and dilatation were present. It is likely that this may have resulted from a combination of the congenital malformation present, of the deformity of the mitral valve, and of the pulmonary vascular lesions.

Although no anatomic mitral stenosis was demonstrated and the circumference of this valve was within normal limits, the mitral leaflets showed fibrosis with rolled cushion deformities of the free margins. The bases of the leaflets measured up to 1 mm. in thickness. The tricuspid valve showed similar fibrous changes, and the ring of this valve was dilated and measured 14 cm. in circumference. It is assumed that the valvular lesion represented a healed inactive rheumatic valvulitis. The thickened valve leaflets and the fibrotic changes in the chordae tendineae could have impaired the function of the mitral valve.

During life this patient presented almost all manifestations which allow a diagnosis to be made with reasonable certainty: (a) marked enlargement of the pulmonary artery with excessive pulsations, (b) increased vascularity of the pulmonary bed, (c) right ventricular hypertrophy with right bundle branch block, (d) a cardiac irregularity closely related to auricular fibrillation.[7] The absence of a murmur over the precordial region adjacent to the auricular muscle may be explained by the large size of the defect. The characteristic "hilar dance" was apparently overlooked on fluoroscopy.

The clinical and pathological diagnosis of an intra-auricular septal defect combined with mitral valvulitis labels the disorder as an example of Lutembacher's syndrome,[8,9] although no anatomic stenosis of the mitral valve was present.   The mitral and tricuspid lesion was apparently acquired during life.

This patient lived a normal life, went through five pregnancies and died when 82 years of age.   Firket in 1880 reported one of the earliest cases with this disorder.   She died in congestive failure at the age of 74 years having had eleven pregnancies.[10]   So far as we were able to determine, the oldest patient prior to this report demonstrated to have an open auricular communication larger than 1 cm. in size has been reported by Roesler.[3]   This subject died at the age of 77 years.   The average age at time of death in his extensive series was 36 years; in another series by Baerrett and White it was 37 years although these authors state that one-half of their patients lived beyond the age of 50 years.[1] It is of interest that in Roesler's series the average survival of subjects with auricular septal defect without associated mitral stenosis was considerably less than that of subjects in whom the defects were associated with mitral lesions. Most patients reported have died following a prolonged state of chronic congestive heart failure.

The patient presented in this report represented the typical clinical, radiologic, and electrocardiographic evidence of an intra-atrial septal defect associated with mitral valvulitis succumbing to intractable heart failure at an advanced age.   A congenital malformation of the heart and particularly auricular septal defects must be included in the diagnostic considerations of congestive heart failure in the aged.

SUMMARY

1.   Clinical and pathological observations are presented in an 82-year-old woman who died in congestive heart failure.   A large interauricular septal defect was present which was associated with mitral and tricuspid valvulitis.

2.   This appears to be the oldest patient on record with such a disorder, but longevity in the face of this type of congenital malformation is not uncommon.

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Book Reviews

A Primer of Venous Pressure. By George E. Burch, M.D., Henderson Professor of Medicine, Tulane University School of Medicine; Senior Visiting Physician, Charity Hospital; Consultant in Cardiovascular Diseases, Ochsner Clinic; Visiting Physician, Touro Infirmary, New Orleans. Philadelphia, 1950, Lea and Febiger, 174 pages. Price $4.00.

This monograph presents a good outline of the problems of venous pressure. It deals with fundamentals and is a book that should be in the hands of all those who contemplate seriously a study of the important part which the venous system occupies in the general circulation.

It is divided into five parts dealing in succession with Functional Anatomy; Physiologic Characteristics and Hemodynamic Phenomena of the Circulation in Veins; Measurement of Venous Pressure; Normal Values of Venous Pressure; and The Venous Pressure in Certain Abnormal Clinical States.

The first three quarters of the volume are devoted to the first four subjects, and the last quarter to clinical studies. This would seem to indicate that there is much yet to be known about venous pressure and that many of its aspects are still controversial.

As the author states, the monograph is intended for the beginner, and, as such, carries him to a certain point from which, if he wishes to study the subject further, he should consult the original texts, which he must unearth for himself as no bibliography is given.   J.C.M.

Coronary Circulation in Health and Disease. By Donald E. Gregg, M.S., Ph.D., M.D., Chief Research Physician, Medical Department, Field Research Laboratory, Fort Knox, Kentucky. Philadelphia, 1950, Lea and Febiger, 227 pages. . Price $4.50.

This excellent monograph is a valuable addition to the literature on the coronary circulation and the myocardium in health and disease.

The experimental basis for the understanding of the coronary circulation is given in a systematic and clear manner. The author is not dogmatic. In cases of doubt, he gives both sides of the question and allows the reader to arrive at his own conclusions or, if interested, to pursue the subject to original sources. He is conservative in his application of our knowledge of the coronary system and the blood flow to cardiac disease. This is as it should be as it leaves the realm of the unknown to be explored further, but, at the same time, it presents a challenge to cardiologists and internists to give more critical study to the coronary circulation in health and disease in man. It may be that new techniques are required. If so, this should not be beyond the ingenuity of clinical research.

There is an excellent and comprehensive bibliography.   J.C.M.

Hemorrhagic Disorders: A Guide to Diagnosis and Treatment. By Paul M. Aggeler, M.D., Assistant Clinical Professor of Medicine, and S. P. Lucia, M.D., Professor of Medicine, University of California Medical School. Chicago, 1949, The University of Chicago Press, 112 pages. Price $10.00.

This is rather a unique monograph on hemorrhagic disorders. It has taken full value of the pictorial method, and, by graphs and illustrations, places each one of the hemorrhagic diseases in an appropriate division.

There is also a chapter upon the Physiology of Hemostasis and another on Hemostatic Tests. Finally, there is a detailed consideration of the various therapeutic agents and procedures. The whole is very well served by a good bibliography, which is arranged under subjects and Authors and is further enhanced by a brief but specific index.

The book, however, is not designed for hematologists but rather for the practising physician, the medical student, and the laboratory technician. This being the case, controversy is conspicuous by its absence, but this serves a good purpose as the test does not lead to confusion and is straightforward and practical.   J.C.M.